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AMERICAN JOURNAL of PHARMACY

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A Record of the Progress of Pharmacy and the Allied Sciences

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THE AMERICAN
JOURNAL OF PHARMACY

VOL. 99 SEPTEMBER, 1927 NO. 9

EDITORIAL

THE RECIPE BOOK

THE LONG-HERALDED Recipe Book of the American Pharmaceutical Association is at last in the printers' hands. For a great many years various workers have contributed their efforts in the compilation of the valuable collection of formulas and finally these recipes have been gathered together, classified, standardized and tested as to workability and reliability—and all that remains to be done now is the printers' job—and proofreading.

Originally suggested by Dr. Henry P. Hynson of Baltimore as an unofficial formulary for the practicing druggist, and as a resting place for the formulas of those preparations, still useful and used, yet dismissed from the official books—the book in its preparation has passed through many hands, and in its present state it stands, no doubt, as the most complete and systematic book of its kind available.

Although the edition now on the press is the first, the Recipe Book is quite worthy of the association that sponsors it.

Possibly a brief review of its contents will reflect the scope and character of the book. The total number of formulas will be somewhat in excess of the figures stated below, taking into account a few recent acquisitions. Each formula is accurately given—in the manner of the National Formulary—and working directions are given for every separate item. The arrangement in each department is alphabetical—based on the English title—ampuls, balsam, cataplasms, etc., in the pharmaceutical section, following in sequence.

The general make-up of the book as far as formulas are concerned is as follows:

	Separate Items
Pharmaceutical	777
Technical	69
Cosmetics	184
Diagnostic Reagents and Clinical Tests	66
Photographic	45
Dental	34
Veterinary	28
Flavoring Extracts	45
Hospital	375
	1623

It was deemed wise to separate the hospital formulas from the bulk of pharmaceutical formulas. Hospital pharmacists will find the book indispensable and every practicing pharmacist should find it a most useful laboratory adjunct.

No longer need Druggist Brown be thinking that Benedict Solution is like benedictine, a cocktail ingredient, or that Mittendorf's spirit is an eye-opener (which it really is—"Spirit Ophthalmicus Mittendorfii"). Such formulas he will have at hand for here is a book that represents an effort to compile all the practical and the called-for pharmaceutical and near-pharmaceutical recipes.

Nor does the book bear the inflexible mark of the official books, upon its contents—for the formulas here permit elaboration—and possibly improvement at the hand of the intelligent operator.

For pharmacists everywhere—in retail stores—in pharmaceutical manufactories—in clinical and chemical laboratories—in the hospital pharmacy—everywhere that pharmacy is practiced this book is *bound* to be invaluable.

IVOR GRIFFITH.

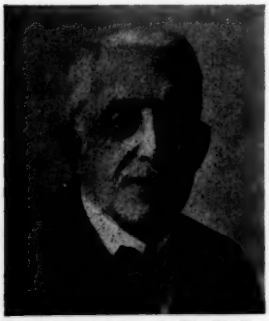
SELECTED EDITORIAL

REVISING THE PHARMACOPŒIA.

APPARENTLY some misunderstanding as to the exact nature of the United States Pharmacopœia has given opportunity for criticism of the work of the Revision Committee, particularly of the Subcommittees on Scope and Nomenclature. In a recent statement, Dr. Horatio C. Wood, Jr., replies specifically to the charges of Dr. H. H. Rusby that the committees have departed from the original principles of the Pharmacopœia. Dr. Rusby has insisted that the committee recommends to the medical profession drugs for which it possesses a special favoritism and has created a false belief in foreign countries to the effect that drugs not in the Pharmacopœia are not used in this country. Dr. Wood rightly dismisses the second charge as preposterous and ludicrous. He takes exception, furthermore, to the dictum of Dr. Rusby that only insufficient use can justify the exclusion of a drug. The first edition of the United States Pharmacopœia, published in 1820, expressed the purpose of selecting from among the substances used in medicine those remedies most worthy of medical employment. To any one at all familiar with the progress of the U. S. Pharmacopœia, it is obvious that it tends more and more to become a scientifically reliable work, to realizing more and more greatly the necessity for established proof of virtue before admission can be granted. The work of Dr. Horatio C. Wood, Jr., as chairman of the Subcommittee on Scope, which was mainly responsible for additions and deletions, and as a member of the Subcommittee on Nomenclature, has been of outstanding importance in achieving this aim.—(*Jour. A. M. A.*, Aug. 27, 1927.)

A WORTHY PHILADELPHIAN

THIS IS Dr. Henry Leffmann's week. He will be eighty years old on Friday, and it is a great pleasure, in felicitating him, to add that we hope he will make it at least ninety. Some time ago he said: "I would like my biography to begin as follows: 'Henry Leffmann was born on September 9, 1847, in Philadelphia. His ancestry on his father's side is partly Jewish; on his mother's side, partly Welsh Hicksite Quaker. He was educated in the public schools, completing his course of B. A. at Central High School, Philadelphia, and receiving the degree of M. A., honoris causa.'" He then added: "In these days of genetics and eugenics, it is worth while to show that a mongrel may have some merit."



Henry Leffmann, A. M., M. D.

As a chemico-legal and medico-legal expert Dr. Leffmann has been identified with Philadelphia life since his graduation in medicine in 1869. It would take a book to tell of the books and pamphlets and papers he has written; and he has been connected in his professional capacity, or as trustee, with most of the learned institutions of the city—Jefferson Medical College, the Pennsylvania College of Dental Surgery, the Philadelphia College of Pharmacy and Science, the Woman's Medical College, the Wagner Free Institute of Science, and the Franklin Institute. He has been port physician and president of the County Medical Society, as well as of the Engineers' Club. Some of his chemical discoveries are well known. But not content with these activities, Dr. Leffmann has long been famous for his contributions to literature and for his well-wrought monographs on American history. Franklin himself was not more active.

There is another point that ought to be brought out in this brief notice of one of our chief celebrities. So genial is his spirit, so friendly and fine, that Dr. Leffmann, during his long life, has made many distinguished friends and undergone many important and interesting experiences; and these ought to be made the subject of a volume of reminiscences of Philadelphia and Philadelphians. Let us hope he will write such a book for the delectation of posterity. What's eighty, after all!—*Philadelphia Record* (Sept. 7, 1927).

ORIGINAL ARTICLES

ISOLATION OF NICOTINE FROM NICOTIANA ATTENUATA, Torr.

By James Fitton Couch

Contribution from the Pathological Division, B. A. I., Washington, D. C.

NICOTIANA ATTENUATA, TORR. a native species of tobacco, occurs according to Tidestrom [4] from Texas to California and Utah. This plant is of interest for its possible poisonous properties and as a possible source for commercial nicotine. The plant has not previously been subjected to chemical examination.

About two kilograms of whole dried plant were available for study. This material was collected by Dr. C. Dwight Marsh and Mr. A. B. Clawson at a place near Panguitch, Utah, on August 15, 1926, when the plant was in seed. The fresh plant was air-dried and shipped to Washington for exact study. Samples were submitted to Dr. S. F. Blake and Mr. W. W. Eggleston of the Bureau of Plant Industry who identified it as *N. attenuata.*

The Alkaloid Content of the Dried Plant

Specimens of the leaves, stems, and roots were separated for alkaloidal determination. These were dried at 100° C., ground to fine powders and the total alkaloid present was determined according to the method of R. R. T. Young.[5] The results were calculated as nicotine. In order to check the analysis and to determine whether non-volatile alkaloid was present, a sample of the leaves was analyzed according to the very accurate method of Chapin.[1] The results obtained by Chapin's method made it apparent that there is no non-volatile alkaloid present in *N. attenuata.* Table 1 presents the results of these analyses. The figures represent percentage of total alkaloid in plant dried at 100° C.

The proportion in the growing plant cannot be calculated as no information was available concerning the weight of the undried plant, but it may be roughtly estimated that the plant loses about 80 per cent. of moisture. This would make the proportion of alkaloid quite small in the growing plant. Inasmuch as the plant was in seed when

collected it is to be expected that the proportion of alkaloid in the herbaceous portions would be smaller than in younger specimens.

TABLE 1

TOTAL ALKALOID IN N. ATTENUATA, CALCULATED TO DRY PLANT

	METHOD	
Part of Plant	*Young's Per Cent.*	*Chapin's Per Cent.*
Leaves	1.46	1.40
do	1.44	1.41
Stems	0.48	
do	0.48	
Roots	0.25	
do	0.25	

Isolation of the Alkaloid

A total of 1340 g. of the dried plant were extracted with 16 liters of boiling water acidified with 25 cc. of acetic acid. The decoction was drained off, and the residue was extracted with a second portion of 16 liters of water acidified with 25 cc. of acetic acid. After standing over night the solution was drained off and the residue was extracted in the same way with 15 liters of boiling water. The third liquid gave no test for alkaloids. The three solutions were mixed and evaporated to 8250 cc. Six hundred thirteen cubic centimeters, equivalent to 100 g. of plant, were reserved and the remainder was placed in a copper still, diluted with water, and was made slightly alkaline with solid calcium hydroxide. The alkaloid was then distilled out of this mixture with steam.

The distillate was made slightly acid with oxalic acid and was evaporated to dryness. The residue was extracted with boiling alcohol which dissolved the alkaloidal oxalate leaving a considerable residue of ammonium oxalate. The alcoholic solutions were allowed to evaporate in air and deposited a small quantity of crystals. The main residue, however, consisted of a brownish, amorphous mass. This was made alkaline with 20% NaOH and shaken repeatedly with ether. On evaporating the ether solutions a light brown liquid of penetrating nicotine-like odor, remained. This did not solidify on standing. It was identified as nicotine by the procedure described below.

The residue in the still from which the alkaloid had been distilled was collected and examined for non-volatile alkaloids. These were not found. The mixture responded to qualitative tests for citric and malic acids and a small proportion of potassium nitrate was isolated and identified.

Identification of the Alkaloid as Nicotine

The quantity of alkaloid was too small to permit determination of the boiling point or optical activity. It gave positive reactions with epichlorohydrin and with ethereal solution of iodine. Its aqueous sloution was levorotatory and when this was neutralized with hydrochloric acid the solution of the hydrochloride was dextrorotatory, a characteristic phenomenon with nicotine and its salts.

The picrate was prepared by mixing aqueous solutions of the alkaloid and picric acid and adding a few drops of hydrochloric acid. The light yellow precipitate was filtered off and dried over sulphuric acid. It melted at 218-219° C. Pinner and Wolfenstein give 218° C.[2] for nicotine picrate.

The salicylate was prepared by mixing ethereal solutions of the alkaloid and of nicotine and extracting the salt with water. On evaporation of the water the salt remained as a reddish oil that soon crystallized in long needles. It was recrystallized from water and dried. It then melted at 116°, a trifle lower than the correct melting point which, according to Schmidt,[3] is 117.5°.

The molecular weight of the alkaloid was determined by titration. 0.2706 g. of alkaloid required 16.64 cc. of N/10 HCl for neutralization. Mol. wt. calc. 162.18, found, 161.6.

The optical activity of the alkaloid in aqueous solution was determined. One decimeter of a solution containing 5.4116 g. of alkaloid in 100 cc. rotated the plane of polarized light 4.23° to the left, whence $[\alpha]^{25}_{D}=-78.17°$. To compare this figure, a solution was made from an authentic specimen of nicotine, a laboratory sample that was not specially purified for this comparison. Treated in the same fashion one decimeter of a solution containing 5.3796 g. in 100 cc. rotated the plane 4.16° to the left, whence $[\alpha]^{25}_{D}=-77.33°$ for nicotine, sufficiently close to the figure obtained with the alkaloid from *N. attenuata* to identify the two bases.

Toxicity of Nicotine

The accompanying tables, 2 and 3, present the results obtained in determining the toxicities of two samples of nicotine. The results in table 2 refer to the alkaloid isolated from *N. attenuata* and those in table 3 refer to the authentic specimen of nicotine mentioned above. The alkaloids were dissolved in sterile distilled water and adjusted to nearly the same concentration. Doses were administered to guinea pigs by intraperitoneal injection, a standardized syringe being used. The results of these tests showed the pharmacological identity of the two samples. The lethal doses were the same within the limit of experimental error and the symptoms exhibited by the poisoned animals were the same in both cases.

Summary

Nicotine has been isolated from *N. attenuata* and has been shown to be chemically and pharmacologically identical with nicotine from *N. tabacum*. *N. attenuata* contains the following amount of nicotine in anhydrous samples: Leaves, 1.45%, stems, 0.48%, roots, 0.25%. The lethal dose of nicotine injected intraperitoneally in guinea pigs was determined as 17 to 20 mg./Kg.

TABLE 2

TOXICITY OF NICOTINE FROM N. ATTENUATA TO GUINEA PIGS

Guinea Pig		*Dose Given*			*Dose mg/Kg. and Effect*		
No.	*Wt. Grams*	*cc.*	*Concent. mg/cc.*	*mg.*	*Lethal*	*Toxic*	*Non-Toxic*
311	480	1.	54.	54.	112.3		
312	480	0.5	54.	27.	56.1		
315	470	0.5	21.6	10.8	23.		
317	500	0.5	21.6	10.8	21.6		
319	505	0.5	21.6	10.8	21.3		
313	510	0.2	54.6	10.8	21.1		
320	515	0.5	21.6	10.8	20.9		
314	515	0.5	do.	10.8	20.9		
316	515	0.5	do.	10.8	20.9		
326	485	0.45	do.	9.72	20.0		
327	505	0.45	do.	9.72		19.2	
313	470	0.4	do.	8.64			18.4
327	505	0.425	do.	9.15		18.1	
325	480	0.4	do.	8.64	18.0		

Guinea Pig		*Dose Given*			*Dose mg/Kg. and Effect*		
No.	*Wt. Grams*	*cc.*	*Concent. mg/cc.*	*mg.*	*Lethal*	*Toxic*	*Non-Toxic*
317	500	0.4	do.	8.64		17.2	
319	505	0.4	do.	8.64		17.1	
318	510	0.4	do.	8.64	17.		
314	515	0.4	do.	8.64		16.8	
320	515	0.4	do.	8.64			16.8
323	500	0.35	do.	7.56			15.1
322	500	0.3	do.	6.48		12.9	

TABLE 3

TOXICITY OF NICOTINE TO GUINEA PIGS

Guinea Pig		*Dose Given*			*Dose mg/Kg. and Effect*		
No.	*Wt. Grams*	*cc.*	*Concent. mg/cc.*	*mg.*	*Lethal*	*Toxic*	*Non-Toxic*
310	480	0.5	21.1	10.55	22.		
309	495	0.5	21.1	10.55	21.3		
322	500	0.5	21.1	10.55		21.1	
306	530	0.5	21.1	10.55	19.9		
323	500	0.45	21.1	9.50		19.0	
325	480	0.4	21.1	8.44		17.6	
324	485	0.4	21.1	8.44	17.4		
308	435	0.35	21.1	7.38	17.0		
321	500	0.4	21.1	8.44	16.88		
323	500	0.4	21.1	8.44			16.88
325	480	0.35	21.1	7.38		15.4	
322	500	0.35	21.1	7.38		14.7	
308	435	0.3	21.1	6.33		14.5	

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(1) Chapin, R. M. 1911. The Determination of Nicotin in Nicotin Solutions and Tobacco Extracts. Bur. Animal Ind. Bul. No. 133.

(2) Pinner, A., and Wolffenstein, R. 1891. Ueber Nicotin. Ber. d. d. chem. Ges. 24, 61.

(3) Schmidt, E. 1911. Pharmazeutische Chemie. Braunschweig, v. 2, p. 1569.

(4) Tidestrom, I. 1925. Flora of Utah and Nevada. Contributions U. S. Nat. Herbarium. 25, 475.

(5) Young, R. R. T. 1927. Determination of Nicotine in Tobacco. *Analyst*, 52, 15.

STUDIES IN THE GENUS MENTHA

13. An Examination of an Oil of Mentha Piperita L. Produced in 1924 [1]

By Samuel M. Gordon [2]

THE CLASSICAL examination of the oil of *Mentha Piperita L.* (Peppermint) is that of Power and Kleber.[3] They isolated no less than seventeen substances. Painstaking as this investigation was, it still left an appreciable percentage of the oil unaccounted for, and did not satisfactorily explain all the differences in oils from different sources.

Since that time the investigation of the oil has been carried out in more detail, in this laboratory. Besides the study of the oil, the water soluble products from the oil have been studied by Emerson R. Miller [4] and by R. E. Kremers.[5] In addition to the compounds isolated by Power and Kleber, these investigators showed the presence of formaldehyde, acetone, methyl and ethyl alcohol, furfural, ammonia and methylamine, with ethyl alcohol preponderating.

Later investigations of the oil and of the cohobated liquors have revealed the presence of methyl-1-cyclohexanone-3, pulegone, and Δ^1, menthene-one 3.[6]

Since the ultimate purpose of this series of studies is the elucidation of certain phenomena, presumably hereditary in nature, it is a matter of prime importance to know the exact composition of a particular strain of Mentha piperita oil and the limits of its seasonal variations.

Material.—The oil used in the present investigation was derived from the strain of Mentha piperita L. which has been grown for a number of years in the gardens of the Wisconsin Pharmaceutical Ex-

[1] Contribution from the Wisconsin Pharmaceutical Experiment Station, Madison.

[2] Wrigley Fellow, 1924-26.

[3] *Pharmazeutische Rundschau*, 12 (1894), 157.

[4] Circular 7, September, 1919, and Circular 9, February, 1920, U. of W. Pharm. Expt. Sta.

[5] Circular 11, October, 1920, University of Wisconsin Pharm. Expt. Sta.

[6] R. E. Kremers, *J. Biol. Chem.* 52 (1922), 443; also *Am. J. Pharm.* 97 (1925), 657.

periment Station. Approximately one liter of the original oil was used for the present study.

Characterization of the Oil.—The following values were determined to characterize the oil:

Density at 25° C.	0.9088
Index of Refraction	1.465
Optical Rotation in 1 dcm tube	—13.25°
Acid Number	0.00
Ester Number	29.22
Ester Number after acetylization	154.7
Ester per cent.	10.32
Combined Menthol, per cent.	6.46
Total Menthol, per cent.	49.52
Free Menthol, per cent.	43.10

Examination of the Oil.—The oil was deprived of as much free menthol as possible by exposure to freezing winter temperatures. 1039 grams of the oil were placed in a separatory funnel and set in the cold until separation by this means was no longer profitable. Only a few grams of menthol were obtained in this way. The drained mother liquors were distilled under reduced pressure with the following results:

Fraction	I	—75° C/5 mm.	149.5 cc.
	II	75-95°/5 mm.	813.2 "
	III	+95/5 mm.	70.3 "

The middle portion (which presumably contained the compounds in the boiling point range of menthol) was again subjected to the freezing process. A considerably greater amount of free menthol separated due to the removal of the terpene compounds contained in fraction I. After the maximum amount of free menthol had been frozen out in this way, the drained mother liquors were again fractionated.

Fraction	B. P./5 mm.	Gms.
I	—80°	8.0
II	80-83°	266.8
III	83-87°	122.5
IV	87-90°	14.5
V	Residue	5.0
Total		522.1

The residue (fraction V) was united with fraction III of the first distillation and treated as described below.

The fractions were placed in different separatory funnels and the freezing process again repeated. No separation of menthol took place, even after seeding each fraction with a few crystals of menthol. This behavior is, indeed, difficult to understand and will require further study on a larger scale before an explanation is forthcoming.

As a result of the "freezing-out" process 139.0 or about 13.4% of pure menthol were obtained. R. E. Kremers [7] was able to obtain about one-eighth of the total free menthol by freezing treatments. The agreement in both studies is very close and indicates a common mechanism hindering the crystallization of the menthol. This behavior is in accord with the well-known fact that removal of any appreciable amount of menthol by "freezing-out" is a matter of considerable difficulty. Kremers is of the opinion that alcohols, possibly iso-menthols, are present in the menthone-menthol fraction which inhibit the crystallization, even from high concentrations. Experiments were made to determine the presence of other alcohols but without marked success.

The individual fractions were next assayed by the neutral sulphite method [8] to determine the amount of ketones, other than menthone. Ten cubic centimeters of oil were used for each assay.

Fraction	Loss by Volume	% Ketone by Volume
II	0.25 cc.	2.5
III	0.30 "	3.0
IV	0.20 "	2.0
V	0.20 "	2.0

Accordingly fractions I-IV inclusive were combined and digested withs sodium sulphite as prescribed for the assay, however, with slight modifications. Efficient stirring was provided. The reaction was allowed to proceed for several days until no further red color appeared on the addition of a fresh supply of Na_2SO_3. No solid seporated, hence the aqueous layer was separated and treated with solid

[7] *Am. J. Pharm. loc. cit.*

[8] Gildemeister-Hoffman, "The Volatile Oils." English translation by Edw. Kremers, Vol. 1, p. 584 (1910).

potassium hydroxide in small portions until no more ketone was liberated. The alkaline liquor was then steam distilled until no more oil came over. This treatment yielded 23.0 cc. of a yellowish-green oil with a decided odor of pulegone. This amount corresponds to about 2% of the oil used, which is in close agreement with the results of the assays recorded above for the individual fractions.

The physical constants of this fraction before and after drying over Na_2SO_4 were determined.

	Wet Oil	Dry Oil
B. P.	———	221-222°
Density $^{25°}$		
$(\alpha)\ ^{25°}_{D}$	+19.54	+19.54
$n\ ^{25°}_{D}$ (Abbé)	1.4793	1.4800

Wallach [9] records for a sample of pulegone regenerated from the bisulphite compounds,

B. P. 221-222°, D 0.936, N 1.4846

The specific rotation [10] varies between +18.° .9′ and +25° .15′. The oil was further characterized as pulegone by the preparation of bis-nitroso pulegone [11] and the semicarbazone. The bisnitroso pulegone melted at 85° C. (uncorrected). A preparation from pulegone from the Jap-mint raised at this station melts at 81° but a mixture of the two show no depression when melted together. The semicarbazone melted at 171-172°, which agrees with that found by Baeyer and Henrich.[11]

Isolation of L-Menthone.—The residual oil from the bisulphite treatment was analyzed for menthol by acetylization with acetic anhydride and subsequent saponification. An average of two determinations showed 79.57% of free menthol, the remainder assumed to be menthone, 100 grams of this fraction were treated with 15 grams of semi-carbazide hydrochloride and 11 grams of anhydrous sodium acetate. Enough alcohol was added to bring the oil in solution and

[9] Ber. 28 (1895), 1963.

[10] Semmler, *Die Aetherische Oele*, Vol. 3, p. 666 (1904).

[11] Von Baeyer and Henrich, Ber. 28 (1895), 654. They record 81° C. as the melting point of bisnitroso-pulegone. R. E. Kremers (*J. Am. Ph. Assoc.* 10 (1921), 834, however, records 83° as the melting point.

the whole shaken for 24 hours. The separated solid was filtered and weighed 18 grams, which is equivalent to 13 grams of menthone. The semicarbazone melted at 184-185° after recrystallization from alcohol. Wallach [12] records 184° C. The menthone was regenerated by treatment with oxalic acid. 10 grams of the semicarbazone were treated with 15 grams of oxalic acid and steam distilled. The dried oil showed the following properties.

B. P. 205-207 (uncorr.); (*a*) $(a)_D$ =—6.91°; $D_{21}°$= 0.8943; $n_D^{25}°$=1.4490.

Wallach [12] records for menthone regenerated from the semicarbazone B. P. 208° C., D=0.894; n=1.4496.

From the oil which did not react with semicarbazide the following derivatives of menthol were prepared, menthyl 3,5 dinitro-benzoate, M. P. 154°; [13] the *a* naphtyl urethane, M. P. 120° ; [14 14a] and the phenyl urethane, M. P. 108° C.

Examination of the Terpene Fractions.—Attention was next directed to the "terepene fractions, *i. e.* the fraction below the boiling point range of the menthol-menthone fraction. L-*a*-pinene and terpinene were found. Limonene or dipentene were not found,[15] when the proper fractions were tested. No test was made for cineol but its presence was indicated by its characteristic odor. The intermediate fractions were found to consist of menthone and menthol.

Terpinene has not before been isolated from the oil of *Mentha piperita L.* The small amount present precluded the possibility of establishing which isomer of terpinene was present.

Fraction I of the original distillation, weighing 149.5 grams was refractionated.

Fraction	B.P./5 mm.	Gms.	a_D (50 mm. tube)
I	-51	3.6	—5.75
II	51-53	25.6	—4.20
III	53-55	29.7	+0.05
IV	55-61	9.8	+4.40
V	61-65	5.4	

[12] Ber. 28 (1895), 1963.
[13] Cohen and Armes, *J. C. S.* 89 (1906), 1481.
[14] Neuberg and Hirschberg, *Biochm. Zeit.* 20, 445 (1909), record 124-128°.
[14a] Bickel and French, *J. Am. Ch. Soc.* 48 (1926), 746, record 119°.
[15] Power and Kleber, *loc. cit.*

Fraction	B.P./5 mm.	Gms.	a_D (50 mm. tube)
VI	65-75	15.9	+10.15
VII	75-80	12.6	+13.25
VIII	80-85	15.8	+10.43
IX Residue	+85	31.1	———

Since a sharp break occurs in the optical rotation at fraction III, fractions I-IV were combined and distilled at atmospheric pressure through a 12″ Vigreux column.

Fraction	B.P.°C	Gms.	a (50 mm. tube)
1	-165	1.8	———
2	165-170	17.2	—6.60
3	170-175	19.4	—7.87
4	175-180	11.5	—7.08
5	180-185	4.5	———
6	185-195	6.6	+3.05

Fractions 5 and 6 were bulked with dextrogyrate fractions of the previous distillation.

Examination of Individual Fractions.—Fractions 2 and 3 yielded nitrosochlorides which melted at 106° and 101° respectively. The benzylnitrolamine bases prepared from these melted at 122-123° and 116-119°. The small amount (0.1 gm.) of the latter made further purification difficult. The compound whose nitrosochloride melts at 101° and whose benzylamine base melts at 116-119° is most likely a pinene and must not be considered as a new terpene.

Fractions 170-175 and 175-180° had a strong odor of cineol. They yielded liquid products when treated with bromine in glacial acetic acid. Hence limonene is probably not a constituent of the 1924 peppermint oil.[16]

Phellanderene was absent.[16] Fractions 170-175 and 175-180° yielded a nitrosite melting at 150-155°. Terpinene nitrosite melts at 155°.[17] An attempt to further characterize the compound by preparation of the benzyl-nitrolamine was fruitless as a liquid product, which did not crystallize on long standing, was obtained.

The dextrogyrate fractions of the first redistillation were refractionated.

[16] Power and Kleber, *loc. cit.*

[17] Wallach and Gildemeister, Ann. 246 (1888), 282.

Fraction	B.P.°C.	Gms.	α (50 mm.)	D25	$n^{25°}$
1	-190	6.8	+1.25	0.909	1.4617
2	190-195	13.9	+3.87	0.911	1.4612
3	195-200	12.2	+5.50	0.923	1.4613
4	200-205	11.7	+8.63	0.923	1.4613
5	205-210	3.5	——	0.930	1.4621
6	210-220	3.4	——	0.933	1.4630
7	220-225	2.5	——	——	——
8	Residue	4.3	——	——	——

The physical constants do not permit any statement as to the compounds present. However, they indicate oxygenated terpene compounds.

Two cubic centimeters of each of the above fractions gave negative tests for pulegone by the bis-nitroso-pulegone test.

Fractions 2-5 inclusive contained a compound isomeric with menthone, presumably d-menthone. Each fraction yielded a thiosemicarbazone when treated with thiosemicarbazide, according to Neuberg and Neumann.[18]

The thiosemicarbazones melt at 155-157°. Neuberg and Neumann record 157-158° C. for the melting point of menthone thiosemicarbazone. D-Menthone has not been previously indicated in this oil.

Summary.—The present investigation of the oil from a known strain of *Mentha piperita L.* grown at Madison has revealed the following:

1. Only thirteen per cent. of the free menthol can be "frozen out" in spite of the fact that the oil contains about 50% free and combined menthol.

2. The presence of the previously described compounds were confirmed, viz. l-menthone, d-pulegone, l-α-pinene.

3. The presence of d-menthone and a terpinene not previously reported was established.

4. The 1924 oil contains neither phellandrene nor limonene as previously reported.

[18] Ber. 35 (1902), 2053.

AN IMPROVED APPARATUS FOR TESTING THE ACTIVITY OF DRUGS ON THE ISOLATED UTERUS.[1]

(Second Paper)

By Paul S. Pittenger

THE AUTHOR has advocated in his textbook [2] and four papers [3] during the past fifteen years, the use of the isolated uterus method for the standardization of Pituitary Extract.

In the textbook and the four papers previously mentioned he contended that the isolated uterus method was the best that had been proposed and described various apparatus and details of technique employed by him in carrying out these tests.

The various forms of apparatus described in these publications gave very satisfactory results and were in continuous use for many years. During this time, however, their limitations were carefully studied with the result that several details were noted in which marked improvements could be made.

This led to the designing of a new apparatus, which although essentially the same as the others in general principle, has many improvements which lead to greater accuracy and simplicity of operation.

As the U. S. P. *X* makes the Isolated Uterus Method Compulsory for standardizing Liquor Pituitarii, the author has had several requests for the details of the apparatus in use in his laboratory at the present time.

A brief description of this apparatus and the assay method follows:

The complete improved apparatus is shown in Figure 1. Figure 2 is a graphic drawing showing the arrangement of the stock bottle, thermostat, heater, cylindrical vessel and stirrer, within the constant

[1] Read before the Scientific Section, Pennsylvania Pharmaceutical Association, Buena Vista Springs, Pa., 1927.

[2] "Biochemic Drug Assay Methods," p. 91 (First edition published 1912).

[3] "The Application of Some Muscular Tissues Adapted to Physiological Standardization," *Monthly Cyclopedia and Medical Bulletin*, Sept., 1913; "A New Uterus-Contracting Method of Testing Ergot, with Comparison with the Blood-Pressure Method," *Journal A. Ph. A.*, July, 1914; "An Improved Apparatus for Testing the Activity of Drugs Upon the Isolated Uterus," *Jour. A. Ph. A.*, June, 1918; "Isolated Uterus Assay for Pituitary Extract," *Jour. A. Ph. A.*, Jan., 1923.

temperature bath. The labeling of corresponding parts is the same in both figures and will serve to illustrate the following description:

The uterus is suspended in 100 cc. of Locke-Ringer's Solution contained in a cylindrical tube (1), the lower end of which passes through a rubber stopper (2) which fills an opening in the bottom of the outer glass vessel (3) which, when filled with water, forms a constant temperature bath.

The water in the bath is heated by means of a "Hot Point" electric immersion heater (*4*). The temperature of the water is automatically kept at 38 degrees C. by means of a toluol-mercury regulator (*5*) which makes and breaks the circuit to the relay (*6*) which in turn makes and breaks the electric current (110 or 220-volt) from plug (*7*) to the heater. The heat is evenly distributed throughout the water by the high speed turbine stirrer (*8*) which is driven by the motor (*9*).

The lower end of the cylindrical tube is connected by a rubber junction (*10*) to one arm of a glass "T" tube (*11*), one other arm of which is connected by rubber tubing (*12*) armed with a spring clamp (*13*) to a waste pipe by which the cylindrical glass tube may be emptied. The remaining arm of the "T" tube is connected by rubber tubing armed with a spring clamp (*14*) to the lower end of the glass tube (*15*) which passes through the rubber stopper (*16*) which fills the opening in both the bottom of the outer glass vessel and the stock bottle (*17*), which is filled with unmedicated Locke-Ringer's Solution.

Therefore, when the spring clamp (*14*) is opened the unmedicated solution from the stock bottle (17) is forced through the connections just described by air pressure, formed by compression of the atomizer bulb (*18*), into the cylindrical vessel (*1*) containing the uterus.

Into the cylindrical vessel containing the Ringer solution dips a narrow glass tube (*19*). This tube is turned at a right angle about half an inch from its lower end. Into this end is sealed a platinum pin (*20*) for attaching the *lower end of the isolated uterus.* The upper end of the tube is connected by means of rubber tubing, (*21*) to an oxygen reservoir. A constant stream of oxygen is allowed to bubble through a small vent situated at the lower bend of the tube, thus preserving the muscular irritability of the uterus and at the same time stirring the Ringer solution.

The *other end of the uterus* is fastened by means of a small hook connected to a silk thread (*22*) which passes over the wheel of a "Becker" universal lever (*23*). The weight of the counterpoise lever (*24*) is increased by attaching an artery clip (*25*). The tension upon the silk thread may be increased or decreased both by changing the position of the counterpoise lever, which may be moved on its fulcrum and by changing the position of the artery clip on the lever.

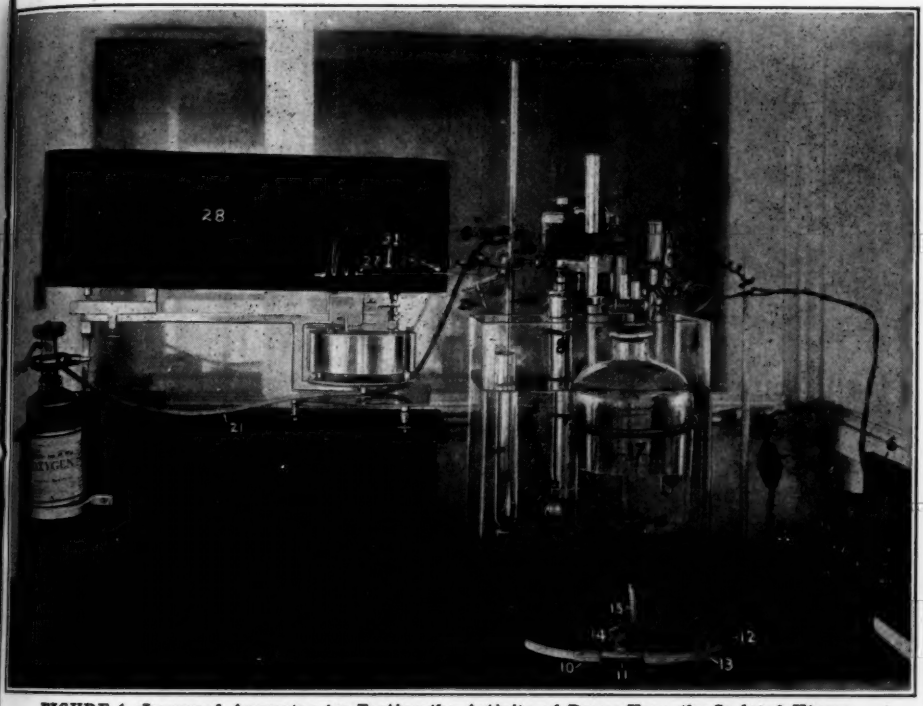

FIGURE 1—Improved Apparatus for Testing the Activity of Drugs Upon the Isolated Uterus.

The end of the writing lever (*26*) is attached to one end of a straw stylet (*31*). To the other end of the straw a celluloid writing point (*27*) is fixed for recording the contractions of the uterus on the revolving drum of the kymograph (*28*).

A thermometer (*29*) is placed in the water bath in order to determine whether the toluol-mercury regulator in maintaining the proper temperature.

It often happens that after suspending a uterus in the oxygenated Locke-Ringer's solution it will relax to a greater extent than was

expected by the operator and the writing point will fall below the smoked paper. Occasionally a uterus will make apparently normal contractions and react readily to the drug, but after two or three doses will suddenly relax to a much greater extent and establish a new normal far below the original. It is not convenient to lower the paper on the double drum kymograph to bring the writing point into proper position. Likewise, it is sometimes impossible to lower the

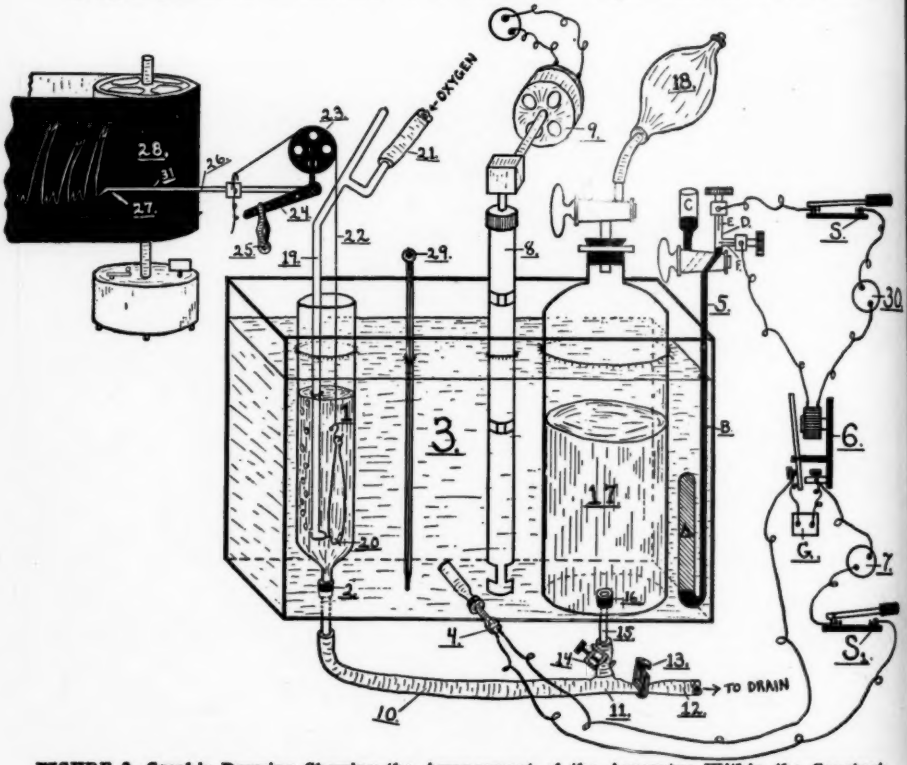

FIGURE 2—Graphic Drawing Showing the Arrangement of the Apparatus Within the Constant Temperature Bath and Method of Connecting the Thermo Regulator (5) With the Relay (6) and the Heater (4).

glass tube (*19*) in order to raise the writing point. In order to make this possible without moving the kymograph or the glass support, the thread (*22*) is tied into a series of small loops about one-eighth inch apart. These loops are attached to the writing lever by placing them over a small hook which is soldered to the writing lever at the point where the straw is attached. The writing point is raised to the desired position and small hook placed through the nearest loop.

Figure 3 shows the construction of the toluol-mercury thermostat. That portion of the glass tube which is lightly shaded represents toluol (*A*) and the black portion (*B*) represents mercury. In order to adjust the thermostat so that it will throw the relay at 38 degrees C. the two reservoirs *C* and *D* are filled with mercury, the stop-cock placed in the position shown and the bulb (*A*) placed in a water bath. The temperature of the bath is increased until the surface of the mercury just touches the platinum contact wire *E*. The stop-cock is then turned to the opposite position (connecting *C* and *B*) and the temperature of the bath adjusted to exactly 38 de-

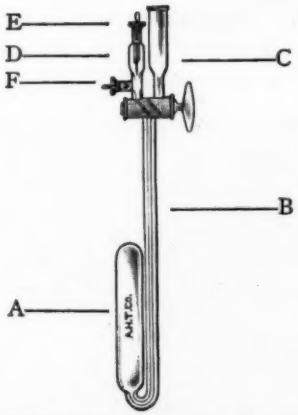

FIGURE 3—Toluol-Mercury Thermostat.

grees C. At exactly 38 degrees C. the stop-cock is again turned to the original position.

The thermostat will then be adjusted so that the mercury will automatically make the connection between the contacts *E* and *F* thus "making" and "breaking" the circuit flowing to the coil of the relay which in turn automatically "makes" and "breaks" the circuit to the heater. Immediately upon completion of an experiment the stop-cock of the thermostat should be turned so that the reservoir is connected with *B*. As the temperature of the water bath falls to room temperature the toluol in bulb A contracts and mercury from reservoir *C* passes into *B*. When the apparatus is to be used again the stop-cock is left in this position while the temperature of the tank is being raised to 38 degrees C. As the temperature of the water in the bath increases the toluol expands and forces a portion

of the mercury back into the reservoir *C*. The temperature should be carefully watched and at exactly 38 degrees C. the stop-cock again reversed so that reservoir *D* is connected with *B*. The thermostat will then automatically maintain the temperature at 38 degrees C.

The platinum contact point *F* is connected electrically with the one side of the coil of the electro-magnet of the relay while the contact point *E* is connected with the one side of the switch, while the other side is connected with the one side of plug (*30*). The other side of the plug is connected with the other side of the coil of the relay magnet.

Before connecting the coil of a relay directly with a 110-volt circuit as described above care should be taken to see that the relay is of the proper type. Many of the stock relays although made to make and break a 110 or 220-volt circuit are equipped with operating

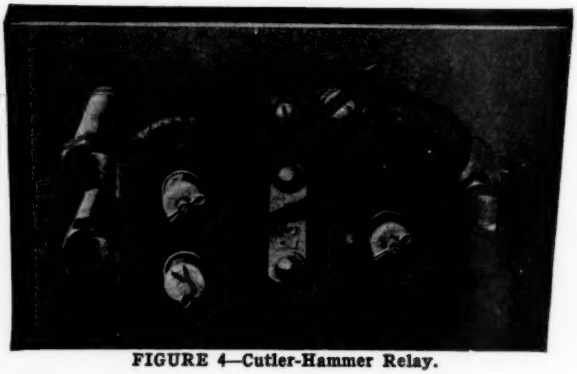

FIGURE 4—Cutler-Hammer Relay.

coils made to be operated by a six-volt circuit. A 110-volt circuit would burn out such a relay. With a relay of this type the coil should be connected with a storage battery or transformer.

With a toluol-mercury thermostat as described it is not advisable to pass a 110-volt lighting circuit through the mercury. The relay used in this apparatus, therefore, is a stock Cutler-Hammer Relay No. 232 (with the contacts normally closed) which has the coil so constructed that it is satisfactory for continuous duty and may be connected direct to the 110-volt circuit. Although the voltage remains the same, the coil reduces the amperage sufficiently to allow the use of the mercury thermostat.

The relay must be of the type which breaks the contact in the circuit to the heater when the magnet is active and closes the circuit

when the magnet is inactive. In other words, when the mercury in the thermostat closes the circuit to the coil of the relay, the relay must break the circuit to the heater and *vice versa.*

As the heater consumes 500 watts a considerable spark is generated at the make and break of the relay unless a condenser is connected with the two contact points. A condenser of a suitable size connected as shown in Figure 5 will absorb the spark and prevent the contact points from pitting and sticking.

The switches (S and S_1) are to break the circuits when the thermostat is not in use.

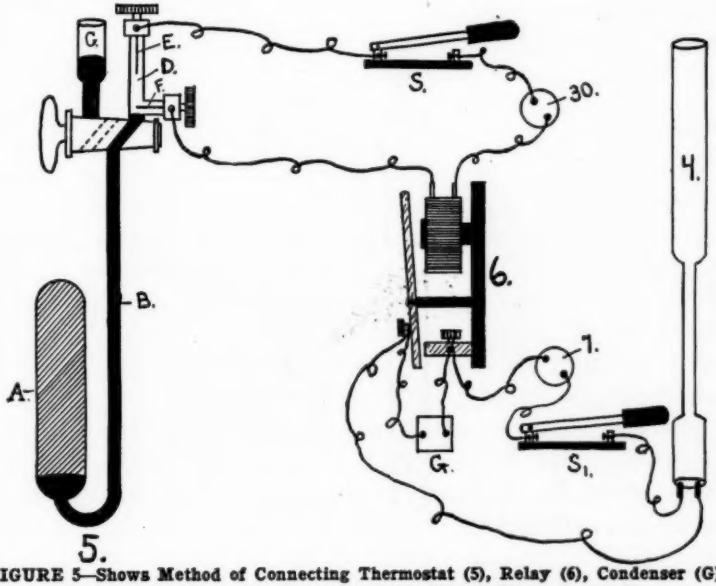

FIGURE 5—Shows Method of Connecting Thermostat (5), Relay (6), Condenser (G), Switches S and S_1 and Heater (4) With Electric Plugs (7 and 30).

In order to automatically maintain the temperature of the bath at 38 degrees C. arrange the apparatus as shown in Figure 5; regulate thermostat as already outlined; start stirrer and close switches. The heater will then produce a gradual increase in the temperature of the water which will cause the toluol in the thermostat to expand and the mercury to rise. When the temperature of the water reaches exactly 38 degrees C. the mercury touches the contact points *D* and *E* which completes the battery circuit and allows the current from the batteries (or transformer) to flow through the coil of the relay, thus forming an electro magnet which lifts the armature of the relay

and in turn breaks the contact which stops the current flowing to the heater.

With the gradual lowering of the temperature of the water the toluol contracts and causes the mercury to fall away from the platinum contact *E*, thus breaking the battery current which is passing through the coil of the relay. This break allows the armature of the relay to fall away from the magnet and make the contact which again allows the current to flow to the heater. The heater gradually increases the temperature of the water until at 38 degrees C. the mercury in the thermostat again makes a contact and the whole operation repeats itself.

FIGURE 6—"Cenco" High Speed Turbine Stirrer.

An even temperature is maintained throughout the bath by the use of a Cenco high-speed turbine stirrer (Fig. 6) which keeps the water in constant circulation without undue agitation.

The accuracy of the Pituitary Assay is to a marked degree dependent upon the uniformity of the temperature of the water bath. The U. S. P. states "The temperature of the bath should be between 37 and 38 dgrees C. but should not vary more than one-tenth of a degree throughout the whole asasy." It is apparent, therefore, that in order to comply with the above strict temperature requirements an automatic temperature control is necessary.

Research Pharmacological Laboratories.

Sharp & Dohme, June 30, 1927.

REPORT OF COMMITTEE ON DRUG MARKET

To

PENNSYLVANIA PHARMACEUTICAL ASSOCIATION

At

Buena Vista, Pa., June 21, 1927

IN REVIEWING the large amount of material submitted by the various members of your committee we are pleased to find that the average condition found during recent years has been maintained. The data given, does not, of course, represent all the analyses made by the laboratories contributing to our report, but represents outstanding results obtained from several thousand analyses performed by members of the committee and their laboratory assistants.

Although the quality of the material examined is generally satisfactory, we are still of the opinion, as expressed in preceding reports, that an improvement in the quality of crude drugs is desirable. Frequently the trouble appears to be due to carelessness, particularly in gathering; such as in the case of a sample of Aletris which upon examination was found to contain 34.72 per cent. of acid-insoluble ash; this high ash content is probably due to adhering earth, but it is a strong indication that no particular effort was made to clean it. In this class of substances we formerly had the resins, gum-resins, etc., but we now find these substances satisfactory as shown by the examination of ten samples of Asafetida, only one of which contained less than the required amount of alcohol-soluble extractive. Five of the seven samples of benzoin were satisfactory; each of the five samples of myrrh and the one sample of kino reported.

Of the relatively few instances of substitution or adulteration found in general analytical examination practically all were found among the crude drugs. Among this class, we find a sample of belladonna leaves that was shown to be almost entirely phytolacca leaves; peppermint leaves containing over 50 per cent. of spearmint leaves and scutellaria that was almost entirely western skullcap.

Probably in this class, should also be placed such cases as that of a sample of Baptisia which consisted almost entirely of stem bases instead of the root; Piscidia which consisted almost entirely of the bark of the trunk instead of the bark of the root; and two samples of Red Saunders that appeared to have been partially deprived of their coloring matter.

Improper storing and length of keeping has an important bearing on the quality of many drugs. In this category we had several samples of Echinacea which had completely lost their characteristic odor and taste; Juniper Berries that were wormy and dirty; Oleoresin Male Fern that was low in crude Filicin and Veratrum Viride that was badly decayed and also contained an excess of stems.

The following substances were examined in the laboratories of the H. K. Mulford Company, Charles H. LaWall and the Smith, Kline & French Company during the period from May 31, 1926, to June 1, 1927:

Acid Hypophosphorous 30%.

One sample had a specific gravity of 1.126 at 25 degrees C. and on assay showed only 19.84 per cent. of Hypophosphorous Acid. The specific gravity of 30 per cent. Hypophosphorous Acid should be about 1.130 at 25 degrees C.

H. C. Luckings.

Acid Phosphoric.

Two samples were found to be unsatisfactory because of the presence of 0.48 per cent. and 0.51 per cent. respectively of sulphuric acid.

T. R. Singer.

Aletris.

The acid insoluble ash of one sample was 34.72 per cent. whereas the N. F. allows only 10 per cent. of acid insoluble ash.

G. I. Davis.

Asafetida.

One lot of powdered Asafetida contained 54.33 per cent. of alcohol-soluble extractive. Nine samples of the gum Asafetida contained: 65.62 per cent.; 63.55 per cent.; 62 per cent.; 55 per cent.; 72.6 per cent.; 63.66 per cent.; 56.29 per cent.; 26.04 per cent. and 62.81 per cent. respectively of alcohol-soluble extractive. The U. S. P. standard is "not less than 50 per cent. of alcohol-soluble extractive."

R. Beresford.

Asafetida.

It is a source of considerable satisfaction to note the quality of the product compared with the low-alcohol soluble and high ash containing products of some years ago. A typical analysis of a sample

of U. S. P. quality is as follows: Alcohol-soluble matter 57.2 per cent.; ash, 6.93 per cent.; acid insoluble ash, 3.59 per cent.

A. F. Murray.

Baptisia.

The examination of one lot showed that it consisted almost entirely of stem bases whereas the N. F. permits only 10 per cent. of stem bases.

G. I. Davis.

Belladonna Leaves.

A local collector offered a sample of Belladonna Leaves which consisted entirely of phytolacca leaves.

G. A. Slothower.

Benzoin.

The following amounts of alcohol-soluble constituents were found in seven samples examined: 72.69 per cent., 74.27 per cent., 75.71 per cent., 75.38 per cent., 77.74 per cent., 87.63 per cent. and 86.11 per cent. The U. S. P. standard is "not less than 75 per cent. alcohol-soluble extractive."

K. Suto.

Calcium Glycerophosphate.

The presence of carbonate and excessive amounts of chloride were found in several lots.

T. R. Singer.

Camphor.

One lot had a specific rotation of—40 degrees at 25 degrees C. and a melting point of 181.5 degrees C. An alcoholic solution was distinctly cloudy. The melting point of U. S. P. Camphor is 174-177 degrees C. and the specific rotary reading —41 degrees to —42 degrees at 25 degrees C.

J. J. Farley.

Caramel.

All lots were of N. F. quality except that they did not comply with the alcohol dilution test. The N. F. states that Caramel is soluble in diluted alcohol, but is precipitated when the alcoholic con-

tent of the solution is increased to 80 per cent. or more by volume. Seven lots showed precipitation in 60 per cent. to 65 per cent. of alcohol.

J. G. Roberts.

Diastase.

It required one sample fifty minutes to completely hydrolyze starch when assayed by the U. S. P. IX Method. Hydrolysis should be complete in thirty minutes.

C. W. Backus.

Digitalin.

An excess of tannin was present in one sample. It also showed an activity of only 88.8 per cent.

G. A. Slothower.

Echinacea.

Several samples of the drug have been offered during the past year that had completely lost their characteristic odor and taste. The N. F. directs that "Echinacea must not be used after it has lost its characteristic ordor and taste."

G. I. Davis.

Gambir.

One lot yielded 81.5 per cent. of alcohol-soluble extractive. The U. S. P. standard requires "not less than 60 per cent. of alcohol-soluble extractive."

H. C. Luckings.

Glycerin.

Of the eleven lots examined one contained an excess of carbonaceous and mineral residue and six failed to comply with the U. S. P. fatty acids and esters test which showed the presence of excessive amounts ranging from the equivalent of .14 cc. to 1.7 cc. of half normal potassium hydroxide volumetric solution.

A. F. Murray.

Guaiac.

The alcohol-insoluble matter in one lot showed an assay of 23.26 per cent. The U. S. P. IX allows only 15 per cent. of alcohol-insoluble matter.

R. Beresford.

Guaiacol.

One lot had a specific gravity of 1.1117 at 25 degrees C. and gave a positive reaction for hydrocarbons. The sample was distinctly purple tinted in color. The specific gravity for U. S. P. Guaiacol is "not below 1.112 at 25 degrees C."

H. C. Luckings.

Hydrastis Herb.

Two samples showed the presence of 1.03 per cent. and 1.23 per cent., respectively, of ether-soluble alkaloids when assayed according to the U. S. P. method for Hydrastis Root.

G. A. Slothower.

Juniper Berries.

Commercial samples have been found unsatisfactory because of being badly worm-eaten and dirty.

G. I. Davis.

Kino.

One sample assayed 72.32 per cent. of alcohol-soluble extractive. The U. S. P. standard is "not less than 45 per cent. of alcohol-soluble extractive."

R. Beresford.

Myrrh.

The following amounts of alcohol-soluble extractive were found in five samples examined: 34.48 per cent., 41.16 per cent., 48.6 per cent., 38.8 per cent. and 50.43 per cent. The U. S. P. standard is "not less than 30 per cent. of alcohol-soluble extractive."

R. Beresford.

Oil of Spike Lavender Flower.

The polariscopic reading of one sample was—3.3 degrees at 25 degrees C. and the specific gravity 0.902 at 25 degrees C. Genuine

oil is dextrorotatory and should have a specific gravity between 0.905 and 0.915 at 25 degrees C.

J. J. Farley.

Oleoresin Male Fern.

Two lots contained only 21.77 per cent. and 21.56 per cent. of crude filicin; Oleoresin of male fern of U. S. P. quality should yield not less than 24 per cent. of crude filicin.

K. Suto.

Peppermint Leaves.

Several samples were offered during the past year that contained over 50 per cent. of spearmint leaves.

G. I. Davis.

Piscidia.

One lot consisted almost entirely of bark of the trunk whereas the bark of the root is desired.

G. I. Davis.

Podophyllin.

Two samples were soluble to the following extent:

Chloroform Soluble Matter.	Ether-soluble Matter.
61.60 per cent.	67.64 per cent.
66.35 per cent.	70.15 per cent.
U. S. P. Standard 65 per cent.	U. S. P. Standard 75 per cent.

H. T. Haefelin.

Potassium Bitartrate.

All samples examined were satisfactory except one sample which contained a high content of insoluble matter.

Jos. W. E. Harrisson.

Potassium Nitrate.

During the past year we have had difficulty in obtaining U. S. P. Potassium Nitrate as well as the C. P. quality that was perfectly soluble. Considerable insoluble fibrous material or lint appears to be present in most of the samples on the market.

H. C. Luckings.

Potassium Sulphate.

An excess of magnesium was found in one sample.

G. I. Davis.

Saunders-Red.

Two samples were very poor in their tinctorial power and had evidently been partially exhausted of color.

G. I. Davis.

Scarlet Red—Biebreich.

One lot had a melting point of 145 degrees C. whereas the N. N. R. states that Scarlet Red Biebreich begins to melt at from 181 to 188 degrees C.

J. J. Farley.

Scutellaria.

The examination of one lot showed that it consisted almost entirely of Western Skullcap instead of the genuine Scutellaria lateriflora.

G. I. Davis.

Soap—Castile.

The iodine number of the only lot examined was found to be only 79 which is below the minimum standard of 84 as required in the U. S. P. This condition has been noted for a long time and may be due to the use of inferior oil in its manufacture.

J. G. Roberts.

Soap—Soft.

An excess of 3.44 per cent. of water was found in one lot which was otherwise of U. S. P. quality. Another lot was found to be slightly below the U. S. P. standard for free alkali.

T. R. Singer.

Umber Burnt.

One sample contained arsenic far in excess of the U. S. P. allowance.

J. J. Farley.

Veratrum Viride.

Two samples were of very poor quality. They contained an excess of stems and the rhizomes appeared badly decayed.

G. I. Davis.

Wax Yellow.

Two lots were of decidedly subnormal quality as shown by the low specific gravity and low acid and ester numbers.

A. F. Murray.

Zingiber.

Five samples yielded the following cold water extractive content: 14.48 per cent., 17.62 per cent., 15.89 per cent., 14.39 per cent. and 13.33 per cent.

J. J. Farley.

The following table shows the sixth report on the weight of unit volume of crude drugs made in the Analytical Department of H. K. Mulford Company, during the year June 1, 1926 to June 1, 1927:

Drug	*Vol. cc.*	*Weight gms.*	*1926-1927*	*1925-1926*
Buckthorn Berries	200	84		
		81.6		
		82.	82.5	
Caraway	100	52		
		49.7	50.8	52
Cardamon	100	62	62	67.5
Celery	100	53.6	53.6	
Cubeb	100	30.9		
		30.8	30.85	
Ergot	200	94.5		
		90.3		
		89.9		
		98.9		
		90.6	92.8	93.2
Larkspur		47.2		
		47.1		
		45.2	46.5	48.8
Sabadilla Seed	100 cc.	49.	49.	
Xanthoxylum	100 cc.	24.6	24.6	

G. A. Slothower.

The following table shows the results of fifty-four crude drug assays made in the Analytical Laboratory of the H. K. Mulford Company during the year June 1, 1926 to June 1, 1927:

Drug	*No. of Samples*	*Lowest Assay %*	*Highest Assay %*	*Standard*	*Number Above*	*Number Below*
Belladonna Leaves	2	.27	.595	0.3% Alkaloid	1	1
Capsicum	6	17.49	28.67	12% non-Vol. Ether Ext.	6	0
Cinchona Red	1	12.22	12.22	5% Alkaloid	1	0
Colchicum Root	6	0.29	0.37	0.35% Colchicine	3	3
Colchicum Seed	2	0.64	0.64	0.45% Colchicine	2	0
Ephedra	4	0.88	0.305	No standard	4	0
Guarana	1	4.29	4.29	4% Caffeine	1	0
Hydrastis	4	2.56	3.84	2.5% Alkaloid	4	0
Ipecac	14	1.36	2.41	1.75% Alkaloid	11	3
Jalap	4	6.96	11.92	7% Resins	3	1
Lupulin	3	67.9	69.66	60% Ether Sol. Ext.	3	0
Nux Vomica	4	2.04	2.85	2.5% Alkaloid	3	1
Pilocarpus	3	0.93	1.44	.6% Alkaloid	3	0
Total	54				45	9

G. A. Slothower.

The following table shows the results of the physiological assay of thirty-six crude drugs made in the Physiological Testing Department at the H. K. Mulford Company during the year June 1, 1926 to June 1, 1927:

Drug	*No. Samples*	*Lowest Assay*	*Highest Assay*	*Above*	*Below*
Aconite	5	166	250	5	0
Cannabis	4	107	120	4	0
Digitalis	15	88	137	13	2
Ergot	4	120	166	4	0
Squill	3	96	120	1	2
Strophanthus	5	53	120	2	3
Total	36			29	7

Therefore, 80 per cent. of the crude drugs were above standard.

P. Masucci and A. Quici.

SPICES

Name	*Accepted*	*Rejected*	*Per Cent. Rejected*
Allspice	3	0	0
Celery Seed	2	0	0
Cinnamon	15	6	28
Cloves	20	5	20
Coriander	5	2	28
Ginger	13	3	18
Mace	12	0	0
Mustard, Yellow	3	0	0
Nutmeg	12	0	0
Paprika	14	1	6.5
Pepper, Black	20	2	9
Pepper, Cayenne	1	0	0
Pepper, Red	4	0	0
Pepper, White	23	0	0

Most all rejections were due to an excess of foreign matter such as dirt or sand except in the case of Coriander where both rejections were due to the fact that the spice contained practically no volatile oil. One rejection of ginger was due to the high content of lime.

Jos. W. E. Harrisson.

Submitted June 21, 1927.

F. J. Blumenschein,
Geo. A. Slothower,
Joseph W. E. Harrisson,
Walter V. Smith,
J. G. Roberts, *Chairman.*

PROPERTIES AND CONSTITUENTS OF AN OIL EXTRACTED FROM THE SEEDS OF DIGITALIS PURPUREA *†

By I. S. Mellanoff, M. Sc.

WHILE investigating the digitonin content of the seeds of Digitalis purpurea, a considerable quantity of the semi-drying oil was obtained. Apparently, the properties of this oil have not previously been determined, therefore the following data is presented.

Description and Physical Properties—An amber colored oily liquid. It has a peculiar fatty odor and has a bland taste.

Refractive Index	1.4755 at 20.0° C.
Specific Gravity	0.9231 at 15.5° C.
Acidity-Figure	9.30
Saponification-figure	207.5
Ester-figure	198.2
Unsaponifiable Matter	6.12%
Soluble Fat Acids	1.66%
Insoluble Fat Acids	90.0 %
Oxy-fat Acids	None
Volatile Fat Acids	4.8 cc. O. I. N $Ba(OH)_2$
Liquid Fat Acids	75.8 %
Refractive Index of liquid fat acids	1.4670 at 20.0° C.
Solid Fat Acids	9.2 %
Refractive Index of solid fat acids	1.4685 at 20.0° C.
Glycerin	11.4 %
Iodine-figure (Hanus)	127.9

*By the author, in this Journal, Vol. 99, 390-401 (1927).

†This paper represents work conducted under a research grant from the F. B. Kilmer Fellowship at the Philadelphia College of Pharmacy and Science, and under the supervision of Dr. Arno Viehoever, Professor of Biology and Pharmacognosy.

NATIONAL PHARMACY WEEK

October 9th to 15th, 1927

THE THIRD ANNUAL observance of National Pharmacy Week will occupy the week of October 9th to 15th. It was decided two years ago, by the American Pharmaceutical Association and the National Association of Retail Druggists, that the second week of October should be observed each year as National Pharmacy Week.

It is anticipated that Pharmacy Week this year will be more generally observed than in the former two years of 1925 and 1926, both of which observances exceeded all expectations. The first Pharmacy Week in 1925 was so successful and the participation by pharmacists all over the country was so general that the members of the committee were delighted and amazed that the interest could be so widespread on a movement which was new and untried. Then in 1926, the second annual observance was increasingly successful and the evidences of the resultant benefits began to manifest themselves in many ways. The story of the second observance which was published in the pharmaceutical journals after the reports from all over the country were received at the national headquarters, told of American pharmacy united in a great movement for public information of mutual benefit to both pharmacy and the public in the interests of a better understanding between the public and its pharmacists, of improved conditions in the practice of pharmacy and of a healthier, happier nation.

The Executive Committee on National Pharmacy Week is composed of ten members representing all sections of the United States. Five of these members are appointed by the president of the American Pharmaceutical Association and five are appointed by the president of the National Association of Retail Druggists. The members of the executive committee are as follows:

N. A. R. D. Committee on Pharmacy Week:
C. Fred Wright, Chairman, Boston, Mass.
A. V. Burdine, Washington, D. C.
John C. Culley, Ogden, Utah.
P. J. Kolb, Chicago, Ill.
Joseph W. Noble, Philadelphia, Pa.

A. Ph. A. Committee on Pharmacy Week:
Robert J. Ruth, Chairman, New York City.
Frederick B. Kilmer, New Brunswick, N. J.
William B. Day, Chicago, Ill.
W. Bruce Philip, San Francisco, Cal.
Hal. E. Duncan, Birmingham, Ala.

The members of the N. A. R. D. and A. Ph. A. Committees selected the writer to act in the capacity of chairman of the joint committees which comprise the Executive Committee and he thus became the national chairman.

The advisory committee, which functions under and in harmony with the Executive Committee, is comprised of all of the secretaries of the State Pharmaceutical Associations. These members of the advisory committee thereby act as the state chairmen in their respective states and are directly responsible for the observance of Pharmacy Week in their states. They may appoint their state committees and as many district and local committees within their respective states as they deem necessary to properly assure the success of the movement. With the organization as outlined above, it can be readily seen that all organized retail pharmacy in the United States is represented and united in working, with the conservation of time, energy and money, to bring about many benefits for pharmacy through the medium of National Pharmacy Week.

The national chairman and members of the executive and advisory committees devote their time to the cause of Pharmacy Week without remuneration. The expenses of the committees are paid from an appropriation of five hundred dollars made jointly by the A. Ph. A. and the N. A. R. D. This sum was made available for the expenses of the 1926 observance of Pharmacy Week. However, the committee carried out an effective well-planned campaign last year and spent less than one-half of the appropriation, leaving a balance sufficiently large to cover the expenses necessary for the 1927 campaign this year.

The editors of the journals of pharmacy and the deans and members of the faculties of the colleges of pharmacy are giving 100 per cent. co-operation in assisting to make Pharmacy Week a magnificent success in October. Without the journals, the committee would be greatly handicapped, because there is no better medium to use in bringing Pharmacy Week to the attention of the retail drug-

gists than by prominent mention of it in the journals of pharmacy. The committee feels deeply indebted to the journals for their co-operation and likewise the individual retail pharmacists should feel grateful to them because the committee asks the support of the journals, the journals carry our message to the retail pharmacists, who in turn broadcast the message of Pharmacy Week to the public, thereby making Pharmacy Week a great movement in the right direction for the uplift of pharmaceutical conditions.

Colleges of pharmacy all over the country will urge their students to help retail pharmacists with their preparations for Pharmacy Week.

The National Wholesale Druggists Association, with Dr. E. L. Newcomb its able secretary, is making the most elaborate plans to assist in carrying the Pharmacy Week message to the public and in spurring retail druggists to participation in the movement. Drug manufacturers and their associations will also render valuable help, as will the Naborhood Stores Association.

Pharmacy Week will be brought to the attention of the thousands of pharmacists who attend the convention of the A. Ph. A. in St. Louis in August and the N. A. R. D. at Kansas City in September.

Practically every retail drug store in the United States has one or more windows. These windows must be dressed very frequently. How can a pharmacist dress his window more appropriately, effectively and with better satisfaction than by putting in a Pharmacy Week window representative of his profession, which is the very backbone of his business and linking his store up with a great national movement which has unlimited possibilities for benefit to his business, his profession, his status and the service which he renders to his fellowmen?

If each drug store in the United States will co-operate, we will have sixty thousand Pharmacy Week windows. Last year we had more than half that many—the State of Missouri had 1102 Pharmacy Week windows competing for the Cloughly Cup of the Pharmacy Week Club of Missouri—the year before they had 372, showing an increase of 730 windows in 1926 over 1925. This year they promise 2000 windows. Philadelphia had 700 windows in 1925 and more than a thousand in 1926.

The drug store windows of the United States offer an invaluable opportunity for pharmacists to disseminate public information. It

is unexcelled location for publicity and if 60,000 window displays carry the Pharmacy Week story the week of October 9th to 15th and during corresponding weeks in subsequent years, then better days are in store for pharmacy. The pharmacist who fails to co-operate is not only missing an opportunity which is placed before him, but he is detracting from the success of the national movement. To dress a Pharmacy Week window should be the very minimum of his effort in co-operation. Many pharmacists will have pharmacy week folders to wrap up with each purchase made in the store; others will have additional comprehensive displays inside their stores. Many local associations and individual pharmacists as well, will run newspaper spreads. Associations especially, will arrange for broadcasting of Pharmacy Week messages at radio stations, and the furnishing of Pharmacy Week speakers at luncheon clubs, Chambers of Commerce, etc.

It is not necessary to neglect the commercial end of the business during Pharmacy Week—in fact, it may receive a natural stimulation resulting from the unusual attention which will be attracted to the drug stores of the nation. However, for a pharmacist to attempt to use Pharmacy Week for plain commercial advertising purposes—attempt commercial exploitation either in his windows or through newspaper advertising, using a Pharmacy Week tie-up, would be plain prostitution of the whole idea, and would react most unfavorably by impressing the public oppositely as to our laudable intentions.

The Committee on National Pharmacy Week is ever willing to be of assistance in offering suggestions for window displays, furnishing copies of addresses to be broadcast or delivered before clubs, etc., copy for newspaper spreads and editorials, etc. You have but to write the national chairman at 80 Beekman Street, New York City.

The Committee on National Pharmacy Week expects the fullest co-operation and observance on the part of every American pharmacist, which will assure success, renew pharmaceutical prestige, and inspire our profession with a needed enthusiasm.

Robert J. Ruth, P. D., Ph. M.

National Chairman,
80 Beekman Street,
New York City.

OUTLINE FOR PHARMACY WEEK PUBLICITY

By N. W. D. A. Committee on Education and Research

1—Copy for full page newspaper advertisement, together with electros and "mats" supplied free by the N. W. D. A. This advertisement to be placed in newspapers and paid for either individually or collectively by wholesalers in each city.

2—Newspapers to be requested to supply advance reprints of page ad. Wholesalers to place advance reprints in hands of all retailers as window posters, same to be displayed during Pharmacy Week. Reprints may be obtained from N. W. D. A. office if desired.

3—Five editorial news stories, one for each day of Pharmacy Week, have been prepared by the N. W. D. A. These are to be given by wholesalers to those newspapers which carry the advertising, with the request that they print the news items.

4—Wholesalers to request newspapers carrying the advertising to send advance copies of the ad direct to retailers, with the request that each retailer make window and counter displays emphasizing pharmacy and promoting the sale of profitable merchandise.

5—Wholesalers to request newspapers to solicit retailers for separate ads. Note: In our First Aid Week campaign one newspaper carried twelve retailers' ads filling the page opposite the page carried by wholesalers.

6—Wholesalers to supply retailers with window strips. Same to be obtained by wholesalers from the N. W. D. A. at cost prices.

7—Wholesalers to reproduce and send to their customers form letter supplied by the N. W. D. A.

8—Wholesalers to arrange with local radio sending stations for a place on the program to give article on Pharmacy Week, supplied by the N. W. D. A.

9—Wholesalers to supply to retailers suggested outlines for window and counter displays, as submitted by the N. W. D. A.

10—Wholesalers to issue to all of their salesmen form letter on cooperating with Pharmacy Week publicity, as per copy supplied by the N. W. D. A.

11—Manufacturers to be requested to reproduce N. W. D. A. Pharmacy Week newspaper ad in magazines, trade publications, or other media, wherever possible. Manufacturers also to be re-

quested to co-operate in placing the N. W. D. A. Pharmacy Week ad in newspapers.

12—Manufacturers and wholesalers urged to use on all of their invoices Pharmacy Week stickers requesting proper window and counter displays by retailers.

13—Manufacturers requested to instruct their salesmen to urge the observance of Pharmacy Week by all retailers.

14—Colleges of Pharmacy requested to assign to advance students the preparation of model window displays in the college laboratories during Pharmacy Week.

15—Pharmaceutical journals urged to reproduce the Pharmacy Week ad and publish summary of activities as presented by the N. W. D. A. and other agencies.

Copy for Pharmacy Week newspaper ad and cuts to go with same supplied free by the N. W. D. A., 51 Maiden Lane, New York City.

Reprints of Pharmacy Week ad and window strips supplied by the N. W. D. A. at a minimum cost price. All other literature described about supplied free of cost.

ABSTRACTED AND REPRINTED ARTICLES

NEW TECHNICAL PROGRESS IN DISINFECTANTS*

By William H. Gesell.

I INTEND to deal first with new developments of the methods of testing disinfectants. No doubt it is known that the present way of evaluation of disinfectants is based upon the method of the determination of the so-called phenol coefficient.

It is not my intention to dwell upon the advantages and the disadvantages of this method. I wish only to point to the fact that there are numerous papers dealing with the subject which indicate that a method of this type is not suited for a general evaluation of disinfectants, since owing to the nature of the chemical substances of which the disinfectant substances are composed, the results obtained

*Read before the Thirteenth Annual Meeting, Insecticide and Disinfectant Manufacturers' Association.

with different substances and different micro-organisms on which the action is tested, must necessarily be different.

The method of the determination of the phenol coefficient according to Rideal Walker and according to the U. S. Hygienic Laboratory uses bacillus typhosus as the test organism. Work with this micro-organism necessitates the upkeep of a bacteriological laboratory and it might therefore be interesting to learn that another method, devised by Luers & Weinfurtner, allows the carrying out of this determination in a much simplier way of observing the inhibitive acton of disinfectants upon fermenting yeast.

Use of the Yeast Method

I wish to add that this yeast method is being used in a somewhat modified manner for the differentiation of strong and mild silver protein compounds. According to the method of Luers & Weinfurtner, the comparison is carried out with a phenol solution of 1:100. Yeast which was brought in contact with this solution is then transplanted into another media and as a rule one observes that such solution does not prevent the fermentation of yeast after three minutes of contact, but the yeast is killed after five minutes. This is regarded as unit of disinfectant action.

A considerable number of papers were published dealing with the relationship between chemical constitution and germicidal action. These studies were carried out on both, substances which are actually used as disinfectants at the present time and upon others which are not yet used for this purpose but are reliable to furnish data on the elucidation of this problem. Researches carried out by Sabalitchka & Dietrich deal with the influence of introduction of substituents into the nucleus of phenols and carboxylic acids. Older reports are confirmed that the introduction of another hydroxyl or carboxyl group into phenols or carboxyl acids reduces the germicidal action. A similar effect is shown upon introducton of sulfo and amino groups into phenols. The introduction of amino groups into cyclic hydrocarbons increases the germicidal effect. The effect of the chlorine depends upon the compound into which it enters. Salt formation considerably diminishes the germicidal action of aromatic acids while the esterification or etherification of some phenols and phenol acids has the opposite effect. These tests were carried out on the micro-organisms penicillum glaucum micrococcus candicans, sarnica flava and b. coli.

A considerable number of data is given on the relationship between the chemical constitution and germicidal action in a paper by Iishiwara. While amino and alkyl derivatives of benzene are practically without effect, the presence of an amino and an alkyl group which are attached to different carbon atoms, lead to a germicidally active compound, *e. g.*, toluidine. Azo and azoxy compounds are actively germicidal. The germicidal action of phenol is increased by the introducton of alkyl groups. Aldehyde groups enhance the germicidal action more than hydroxyl groups. Iodine in combination with organic compounds may increase the germicidal action considerably, but this increase is accompanied by an undesired organotropic effect. The germicidal action of aliphatic organic acids is increased by the introduction of chlorine atoms. Thus aminochloroacetic acid is much more active than acetic acid, but, on the other hand, trichloracetic acid is not more active than the monochlor product. There are many similarities between the germicidal action of inorganic and organic metal compounds, the latter being, however, less organotropic.

Attention should be called to a paper by Cooper and Forstner who distinguish between the physico-chemical and chemical action of disinfectants. According to these authors, phenol interferes with the colloidal state of the protoplasm and it is, therefore, to be regarded as a physico-chemical agent. On the other hand, it is assumed that other compounds, *e. g.*, nitroso derivatives, are purely chemical agents on account of their direct reaction with the organic matter of the micro-organism. Attention should be called finally to a paper by Klarmann which brings the tautomeric configuration of substituted polyphenols in relation with the germicidal action. A number of compounds with high phenol coefficients of the series of dihydroxy diphenyl hydrocarbons is described.

Use of Waste Products

It is one of the foremost tasks of the technology of disinfectants to attempt the preparation of products which would be cheap and thus allow an extended use in daily life. This goal may be reached either by having cheap materials on hand which could be used in larger quantities, or to increase the germicidal action to such an extent that extremely diluted solutions might be used, so that the price of the preparations would not impede their application. It is natural that the preparation of substances which can be used in large quantities presupposes their low toxicity. All industries, including the

industry of disinfectants, must pay attention to the utilization of waste products for their particular purposes. In this connection, it is to be pointed out to the very favorable results which were obtained with the application of chlorinated natural bark extracts and sulphite liquors of cellulose manufacture. Direct application of compounds which contain chlorine in an active form, *i. e.*, in such a state that chlorine is split off in the presence of susceptible organic matter, has attained a rather wide scope.

It suffices to mention that some of the organic chlorine compounds are obtainable in a state of comparatively high purity, solubility and stability. On the other hand, it seems that there are microorganisms which survive the action of chlorine. It is, therefore, necessary to keep this point in mind in disinfecting water of pools or drinking water with active chlorine preparations.

Ammonia-Chlorine Effective

According to researches of Olshewski, the disinfectant with a combination of chlorine and ammonia is more thorough than with chlorine alone. This holds particularly for the purification of river water. The most advantageous ratio is one and one-half parts of ammonia gas to one part of chlorine gas. A further advantage of this method is the elimination of the objectionable chlorine odor.

No particularly new data were obtained on the preparation of disinfectants composed of tar distillates. The coal-tar disinfectants may contain different substances which serve as emulsifiers. A widely used emulsifier is soap, which may be prepared from various sources. More attention must be paid to this problem of soap in coal tar disinfectants with view to some papers on the germicidal action of soaps. Soap is important from two viewpoints—first, on account of its nature as emulsifier and, secondly, as a depressant of surface tension. It is interesting that a differentiation of bacteria may be based upon their ability to grow at different surface tensions. Sodium oleate is best for such experiments in reducing surface tension, while the addition of charcoal increases surface tension.

The outspoken germicidal action of soap is shown in the work by Tilley and Schaffer. Thus saponified cocoanut oil is more germicidal than saponified linseed oil. The germicidal action of soap is increased by the addition of sodium chloride. However, the practical value of the addition of sodium chloride is diminished on account of flocculation in the presence of serum.

Soap and Phenol Ratios

The relation of soap and phenol derivatives is of extreme importance. While the application of cocoanut soap is recommended for mixtures with cresol, it is pointed out that a mixture containing one-half as much soap as cresol shows the maximum germicidal efficiency. A further increase of soap causes a reduction of the germicidal action. Walker showed in an interesting paper that the degree of saturation of the organic acid of the soap is of importance, since different bacteria show a different resistance to soaps. Thus dysentery and paratyphoid bacteria are killed by soaps of saturated fatty acids, but are completely resistant to unsaturated ones. He also recommends cocoanut oil soap for dysentery, paratyphoid and typhoid. Zernik describes an interesting type of disinfectant which is obtained by neutralization of alkaline creosote liquor of bituminous coal distillation with naphthenic or naphthene sulphonic acids. An interesting preparation is a mixture of saponified cresol with chloroform, which, it is claimed, possesses a germicidal action similar to that of phenol but it does not irritate human skin.

These remarks may suffice for a general characterization of progress in the individual groups of disinfectants. We still will have to deal with some synthetic preparations which are regarded as more important. A disinfectant of a comparatively high germicidal efficiency is obtained by mixing ortho or para-dihydroxy diphenyl with suitable organic solvents or soap. It is contained in the distillation residue of synthetic phenol. Fractions of low coal car distillation, boiling between 230 and 300 degrees at ordinary pressure are used for the preparation of disinfectants. A British patent describes the application of furfurol as fungicide and disinfectant. Voille recommends the application of chloropicrine as an excellent antiseptic which is active in dilutions as high as 1:40,000 to 1:80,000. It is claimed to be better than chlorine and iodine. It is stable in sealed containers and has, on account of the extreme dilutions in which it may be used, a comparatively low toxicity. It will be remembered that chlorolicrine played an important role in the chemical warfare of the World War.

The Tellurium Compounds

An extremely interesting group of preparations are the tellurium compounds. It was known that tellurium acid tartrate is as effective as phenol against b. coli or typhosus and that potassium iodotellurite

has a high phenol coefficient in the absence of organic matter. Morgan and Corby showed that cyclo telluro pentane—3, 5—diones are extraordinarily powerful disinfecting agents, the disinfectant action being observed in dilutions as low as 1:1,000,000 to 1:20,000,000. The maximum effect is observed after four hours. In spite of the poisonous nature of these compounds the safety margin is sufficiently large. They retain to a large extent their germicidal effect in urine and are recommended for cystitis and eye infections. Unfortunately, the action is virtually completely lost in the presence of albuminous matter (serum). It is perhaps interesting to point to the germicidal halogen compounds which were prepared by Erlich and Bechhold and had not achieved any importance since their germicidal action is also reduced to practically nothing in the presence of albuminous matter. A number of new preparations were created which contained the metals cerium and thallium respectively as active ingredients. The preparations of isotonic solution of cerium iodide is described in a paper by Potratz. A cerium quinoline compound is recommended as a non-irritant disinfectant instead of tincture of iodine.

Considerable research work has been done generally on the oligodynamic action of metals. The germicidal action of such oligodynamic solutions is assumed to be due to a combination of protein binding and oxygen catalysis and subsequent dehydrogenation. The oligodynamic action is eliminated by reduction of the mobility of ions which may occur on account of oxidation or formation of carbonates.

Fatty Acids—Copper Compounds

Copper salts of fatty acids in paraffin, alcohol, or other organic solvents, except phenol or cresol, *e. g.*, copper oleate in paraffin or vaseline oil, are recommended as effective disinfectants and insecticides. It is shown experimentally that the preparation usually penetrates the bodies of organisms and soon the green coloraton betrays the presence of copper within the body. It is not intended to further dwell upon the metal organic compounds since they do not belong in the immediate sphere of our interest, being of more importance in chemo-therapy. Selenium compounds also found application as insecticides and disinfectants. Among the organic preparations, mention should be made of condensation products of tetra-, penta- and hexa-methylene carboxylic acids with keto alcohols. These products are used for disinfection and destruction of plant parasites and

resemble in their constitution the compounds which form the active principle of so-called Persian insect powders.

It is to be seen from this report that a considerable amount of research remains to be done on the basic principles of all branches of technology of disinfectants and there are still many questions to be elucidated. We may say that we are still rather far from the ideal disinfectant from which we would have to expect a high bacteriotropic and a low organotropic action which would direct itself against all kinds of micro-organisms and would not be impaired by the presence of organic matter. In considering the different nature of the bodies of micro-organisms, it is necessary to find out the cases in which a high liquid solubility is desired and the others where stress is to be laid on chemical reactivity. Since the theory of disinfection has of late attracted considerable attention of both organic chemists and biologists, it is to be expected that quick progress will be made in the future.

INFECTIOUS DISEASES*

By Mathew A. Reasoner, B. S., M. D., F. A. C. S.

Where Did They Come From and Where Are They Going?

THE EVOLUTIONIST accepts in a general way the hypothesis to be presented explaining the development of infectious diseases. On the other hand, I fail to see how even the most ardent fundamentalist can maintain that when Adam and Eve stepped out of the front gate of the Garden of Eden, there already existed such infectious diseases as typhoid fever, smallpox, measles, bubonic plague, scarlet fever, syphilis and gonorrhœa, and particularly those which do not propagate naturally except on or in the human body. If so, where were they and how? It is a fair assumption that when human life began, the world was functioning under the same natural laws which now control. Infectious diseases as such did not exist at the beginning but the potential disease did exist in the shape of non-pathogenic organisms which could only take on disease producing characteristics during close and prolonged contact with man and animals. This contact occurred in the presence of dirt and filth and insanitary surroundings. It is very doubtful, had man always lived a proper and cleanly existence, if some of them would have ever appeared.

The world was apparently so designed that mankind develops best in the face of work, of hardship and adversity. While it may seem a radical statement, yet it is scarcely possible to conceive of a better plan for the development of the human race than the potentialities of disease. This is a punishment which man brings on himself by ignorance, filth, and sin and which can only be avoided by right living and the employment of scientific knowledge gained by laborious research. Infectious disease still remains one of our greatest problems and will be so for years to come. The innocent still suffer with the guilty and the punishment for the sins of one generation still continue to be visited upon succeeding ones. This is in itself a form of evolution which serves to eliminate the unfit. Nations and peoples who live properly will grow in numbers and intelligence and power while those who do not comply with the laws of nature will eventually eliminate themselves.

The characteristics of bacteria are susceptible to change according to their environment. In the beginning of human life there was probably no infectious disease as such but there were bacteria and organisms with potentialities for development and disease production which could appear under favorable conditions. The researches of paleontologists indicate the absence of disease among the animals of the Proterozoic or Huronic Age. Evidences of disease have been found in animals only as far back as the early Paleozoic and probably began in plants and animals about that time in both the old and the new worlds and appear to be a fundamental feature of evolution and development. It is possible to take virulent disease organisms and by growing them in the test tube under varying conditions, to rob them of much if not all of their virulence. It can then be brought back again by inoculating repeatedly into a series of laboratory animals. A German investigator took an ordinary harmless bacterium which grows free in nature but causes no disease but does resemble the bacillus of tuberculosis when stained and examined under the microscope. By repeated inoculations in guinea pigs he was able to develop virulence in the bacteria and produce a disease resembling tubercular peritonitis. He then took the organism and started to grow it again in the test tube, reducing the temperature gradually and in a short time the virulence was all gone. So with diphtheria, tuberculosis, tetanus, grown in the test tube under conditions different from those in the human body, the ability to produce disease becomes temporarily lost in whole or in part.

When mankind was young, it was often necessary to live in caves or very close quarters, with cleanliness as a still unknown virtue. Under these circumstances everything he ate or touched was so well covered with primitive and undifferentiated bacteria that it is to be expected that a few of them would become habituated to living on men and might remain harmless or become disease producing. If a Toxine producer, there was little given off under the preliminary conditions of their first growth. In the meanwhile the host was gradually accumulating resistance as the bacteria grew in toxine producing ability. Bubonic plague probably originated in some such manner in some isolated out of the way corner of Asia. When he starts out to be insanitary no one can beat an Asiatic. It developed through a period of centuries and during this time it did little harm because many generations continually exposed to the disease had been developing a resistance to this particular organism and quite probably many of them never knew they had it. Then along came a band of robbers or a conquering army, the first contact with the outside world. The dogs of the invaders picked up some new fleas as did their masters. They slept in the infected houses and took women and children and dogs and fleas with them. As they went along they infected other rats and squirrels and fleas along the route and eventually struck a channel of commerce. The farther the disease went the more virulence it came to have. We have heard how much more virulent diseases may become when brought to a country for the first time. Measles was introduced into Guam in 1858. At the end of the epidemic there were only 8,000 left of the original 60,000 inhabitants. It was the same way with the American Indian with measles and tuberculosis and other diseases. In the early days, there was relatively little travel from place to place and thus there was afforded an excellent opportunity for the development of immunity on the part of some and vulnerability upon the part of others. In early days when a country set out to conquer the world, they were laying up trouble for themselves which they knew not of and the trouble was dependent largely upon the insects which they acquired and carried with them and distributed here and there and the flies and mosquitoes which they encountered. The early Egyptians knew something about insects and in a papyrus there has been found a list of them. There was found one of their sacred charms which has upon it a conjuration against mosquitoes.

Soap was known to the Grecians and Romans before the time

of Christ and is mentioned in the Bible but was probably not used so much for cleanliness as a medicament and as a preparation for weaving. The Germanic tribes were probably the first to use soap habitually for cleaning the skin. It is probable that its invention came about through the use of wood ashes in cleaning bowls and kettles in which meat had been cooked. It is very probable that many of the heroes of antiquity and celebrated characters of bygone history did not follow any regular practice of washing their bodies, faces, or hands. Probably many of them never did wash their ears or clean their finger nails and doubtless many of them carried a more or less generous assortment of insects around with them. The Egyptian priests were very much of an exception to such a supposition as they washed their bodies three times daily and had their hair cut every three days. Moses, who in my opinion is one of the outstanding figures in all history, learned much from the Egyptian priests by whom he was doubtless initiated into their mysteries. Recently there was recorded in the daily papers the result of a vote in a number of high schools on the greatest ten men in history. Moses did not receive even honorable mention. When such a thing comes to pass there is something wrong with the manner in which history is taught in these schools. Moses certainly belongs in the first division of any such classification. The sanitary teachings of Moses are good today; the book of Leviticus should be read by all sanitarians. Moses is perhaps not up to 1927 in every particular but he is certainly after the Spanish-American War. I think it would have been quite safe to have donned one of Moses's cast off hats, provided he wore such an article and I am positive that Joshua drew no "cooties" with it when he inherited Moses's mantle.

Moses laid down living rules for the Jews and told them they should keep away from other tribes and peoples. Four hundred years after their arrival in the promised land, living meanwhile under the rules of Moses, brought them to the height of their power and prosperity under the reigns of David and Solomon. They were now so prosperous that there was a relaxation from the former strict rules of living. There came about trade and intercourse with foreign countries which was forbidden in Deuteronomy (vii) and there came into the country, along with the strangers, new religions, changed habits and strange diseases. Solomon may have been a very wise man in a literary way and as a business man and an administrator and a builder and it would appear that he must have had a very

winning way with the ladies, but in practical intelligence and judgment concerning the things which were best for his people he was as a small child compared with Moses.

Solomon built something of a water supply near Jerusalem and remains of such structures are found in various countries of the East. They were, however, more of a luxury than anything else. The Greeks did quite a little along this line but the Romans were the first to make of bathing a real indoor sport. That was the time when the Romans were going everywhere and so they scattered their bathing establishments all over what was then the known world. Some of the aqueducts leading into Rome cost several million dollars to construct and the point of it is that they realized the necessity of a water supply sufficiently to spend the required amount of money. The bathing houses and personal cleanliness were, however, largely for the patricians and the slaves and plebeians of whom there were many, were neglected. They had their revenge, however, and a similar one to that of Samson when he pulled down the pillars of the temple. Many long and detailed explanations have been given for the fall of Rome but one important cause is very simple and may be given in the few words, malaria, cholera and bubonic plague. Back any historian up in a corner and he will have to admit it.

The farther people got into the Middle Ages, the filthier their habits became and this period might well be named the "age of epidemics." There were more infectious diseases than ever before or since. In order of importance they were about as follows: Bubonic plague, typhus fever, smallpox, syphilis, cholera, and malaria. The crusaders and the traders and the armies carried these diseases from one place to another. Bubonic plague went from Asia to Africa and appeared in Europe about 1348 and kept on coming in epidemic form until the seventeenth century. It cost the lives of over 60,000,000 people in Europe alone. Bocaccio's "Decameron" is the story of a party who during the epidemic of 1348 sought refuge from the plague by isolating themselves from contact with the world. This is the disease which caused the first quarantine when in Venice, three "quarante giorni" (forty day governors) were designated to control during the disease. The word quarantine thus came to be coined. In 1630 Venice had 500,000 deaths from plague and this precipitated the downfall of this government "whose great fleets once held the gorgeous East in fee." Once again the history of the world was changed by the pestiferous flea and the obnoxious rat.

The Egyptian priests probably understood something of the contagious element of disease, certainly Moses did so. Aristotle and Galen also expressed a similar opinion but no progress was made beyond Moses for almost 3000 years or in 1600 A. D. when Kircher who first used a microscope for this purpose, expounded a theory of microbic action which was approximately correct. Then they went back to sleep for 126 years when Plenciz expressed the opinion that each one of the infectious diseases has its own specific cause. The surgeons were in the meanwhile attempting to get results with the use of boiling oil but the after results were worse than if left alone as was discovered by Paré.

One of the great events of history took place in 1843 when our well known Oliver Wendell Holmes advanced the theory that childbed fever is a contagious disease. Three years afterward Semmelweiss of Vienna proved it beyond all possible doubt. In 1865 Lord Lister gave to the world the practice of antiseptic surgery which in its later development is one of the great blessings of mankind. It is interesting to note that during the years of the Dark Ages there were many investigators attempting to discover the "philosopher's stone" or the secret of eternal youth. They never found what they were looking for but they did give to the world the science of chemistry which has been of the greatest help in the elimination of infectious disease.

I have heard of instances where persons of considerable financial resources have built what have been termed modern and sanitary towns or small cities, where the health of the inhabitants could best be preserved and living conditions made the best and most pleasant possible. If I were possessed of unlimited means and decided to build such an institution, I think I should have it constructed around a large central square and instead of a military monument I should place in this square a large statute of "Moses the Sanitarian." Of course there would be a city park and in this I should have a statue erected to Semmelweiss. I think I should build a fountain and dedicate it the unknown benefactor of the human race who invented scap. There should be a lake in the vicinity which could be named Lake Caesar or Hadrian and an opportunity would be given for all to learn to swim in the Roman Baths. In the library there would be a portrait of Oliver Wendell Holmes. The hospital would be named after Lord Lister and in it there would be portraits of Pasteur and Koch and the high school would be given the name of the discoverer

of the coal tar derivatives. I should name the streets after some of the distinguished ancients as Aesculapius, Aristotle and Galen, some of the middle period as Kircher, Plenciz, Paré, Jenner, Pringle, and Simpson and some of the more modern as Lambl, Laveran, Eberth, Hansen, Pfeiffer, Klebs, Loeffler, Obermaier, Bruce, Behring, Sternberg, Ross, Metchnikoff, Yersin, Reed and Carroll and Gorgas, Ehrlich, Wassermann, Ashford, Jordan, Biggs and Park, Russell, Manson, Kitisato, Noguchi, Wright, Smith, Shick, Dick, Zinsser and many other pioneers having equal claim upon the grateful appreciation of posterity. It would probably be necessary to lay out a few subdivisions in order to have streets enough to go around. I would then hope that the inhabitants and officials of this sanitary city would attempt to live up to the example and teachings of these distinguished persons.

The signing of the Magna Charta is often mentioned as one of the greatest steps in history and justly so; but I wonder if there is not something more fundamental and basic, of which the protest indicated by such a document is only a symptom. It seems to me that the realization by the more intelligent fraction of the people that it was not desirable to be dirty and carry insects around with them or live in the presence of vermin and filth, has been at the bottom of much of the progress of the human race. Under such conditions the development of self-respect and independence was fundamental and the revolt against tyranny was secondary and bound to come about in the natural course of events. Certainly the people of England and the Colonies never worried nearly so much over the tyranny of their rulers as they did over the outbreak of an epidemic of cholera or smallpox.

I have sometimes wondered how one of us would have enjoyed attending a royal banquet of the time of King Arthur or thereabouts. To begin with there were no bath tubs in their houses and they did not realize they were missing anything nor know any reason why there should be any. There was no proper water supply. There was no general method of sewage disposal nor any toilet arrangements as we know them and the less said about the condition of the streets, the better. There were of course no screens and innumerable flies. Handkerchiefs and napkins were not yet invented. A hunting knife and the hands served all necessary purposes for handling the food at table. Rushes were strewn upon the stone floor and removed from time to time with their accumulated debris. The

dogs often came in with their masters and lay upon the floor waiting for bones to be thrown them from the table by their more or less intoxicated masters. Meanwhile, the insects were there in force, some of them flying and some of them crawling, and the mice and rats peered out from dark corners awaiting the departure of the dogs that they might leave their refuge and secure a share of the food.

Of course they did make some attempts to limit the rats and other property destroying vermin as is evidenced by the following voucher for a payment made by the Master General of Ordnance to Charles II. "Whereas Elizabeth Wickley is imployed in killing of Rattes and other vermins in and about His Ma'te's stores and houses in ye Tower of London. I have therefore thought fitt to allow her ye sum of Eight Pounds p. annum. Thomas Chickeley, 30th March, 1672." Elizabeth probably had a real busy time if she took her occupation seriously.

The world is growing better all the time. It may be that our pathway at times resembles a zigzag line but the general trend is always upward. I am willing to admit, however, that a stroll around through many streets and vacant lots of Brooklyn and New York is sufficient to bring a feeling of pessimism to the most enthusiastic.

During the last seventy-five years the chemists have been active in searching for new forms of antiseptics, disinfectants and insecticides and the sanitarians have devoted much time to determining their possibilities. As a result we now have hundreds of these compounds and we have the insects on the run. The only trouble is that they never know when they are "licked" and we must keep everlastingly at it. I mention this point as one of the foundation stones of the present day civilization of the world and the prolongation of human life and prevention of disease.

Yellow fever has been almost eliminated and it is very probable that in time it will be wiped from the face of the earth. Smallpox and typhoid fever are both of them preventable diseases and so easily preventable that anyone who contracts either should be ashamed of it. Three injections of typhoid vaccine will give security for two years or longer and does no possible harm to the individual. Cholera and rabies are conspicuous by their absence, the dysenteries are rarely seen, diphtheria is now so well under control that there is a campaign on to eliminate it from the State of New York and that is not impossible. Scarlet fever is now a preventable disease. And so with

many other of the infectious diseases with the marked exceptions of influenza and the pneumonias and their turn will come sooner or later. Without attempting a detailed statement we may say that it is possible to keep a check over the insect borne diseases if we keep the insects killed off, that we can give immunity to other diseases which will keep them away provided we follow out the necessary procedures, and the amount of all infectious disease will be lessened if people live properly.

The average person wants to do the right thing but sometimes he listens to bad advice. The facts of induced immunity to disease without harmful results and the possibility of cleaning up disease are as easily demonstrated as that two and two make four or that night follows the day or the attraction of gravitation. Our old geometry used to say that "when anyone denies a self evident truth we simply say he is foolish and do not argue with him." Unfortunately we cannot adopt such an attitude in a sanitary campaign.

Human nature is a peculiar institution. In some ways we are like a flock of sheep or the mules of a pack train which follow the bell mare under the mistaken belief that the mare knows more than they do. There is always a small element in society anxious for leadership and who attempt to put themselves in the position of the bell mare by means of noise or bizarre performance. The prevailing reason is that such leadership is financially lucrative. In some cases their mentality is such that they do not appreciate the illogical nature of their teachings and in others they are not concerned with either logic or ethics. They may assume a pseudo-scientific attitude upon a basis of fad, fancy, or foolishness, their facts may be only figments of the imagination and their logic only reiteration. It is strange how many people have been convinced of some statement from having seen it often in print. So, some of the people are led in these diverse channels and another element is merely indifferent or ignorant. The combination of these two elements with a third which is constitutionally "agin the government" is the reason why it will be a long time before we will ever attain a full measure of success in the prevention of preventable diseases. In the meanwhile those will die who do not need to die, there will be suffering which is needless and sorrow which might be prevented. The bright side, however, is that this in itself will become a measure of improvement or natural selection as has always been and the better poised and more intelligent portion will continue to survive in greater numbers and the general average of intelligence will be raised over what it would otherwise be.

THE LOSS OF MORPHINE IN POWDERED OPIUM BY KEEPING: ITS CAUSES AND PREVENTION*

By A. C. Abraham, Ph. C., F. I. C., and J. Rae, F. C. S.

IN THE last paper, which we published on this subject (*P. J.*, July 14, 1923), we suggested as a working hypothesis that the alterations which we and others have found in the morphine content of powdered opium when kept were due to the more or less free access of air, and to elucidate, if possible, this question we proposed to carry on some further experiments, but especially we wished to find some process which would stabilise opium powder. We therefore decided to test the same sample of opium on which we had been working previously, and of which there were some pounds left, and then to put away bottles each containing 8 Gms., treat them in different ways and test them at intervals of three or four months.

The first series A were simply placed in full ½-oz. N.M. vials and well corked.

A second series B were left in four similar bottles plugged with cotton wool.

Series C consisted of eight bottles. They were heated in a water-oven (temperature 98 degrees), and then sealed with paraffin.

The fourth series D were put in similar bottles, but we passed carbonic acid through them for a few minutes, sufficiently long as we thought to remove all air, and then sealed them.

Series E were similarly treated with oxygen and sealed.

Unfortunately our results from all these series have been interfered with by two unforeseen causes. First, there was an unfortunte circumstance which, at the time, we thought could not have any material effect on our experiments, which we think it desirable to explain fully.

When this opium was first powdered and put through a 24 sieve, it should, according to the test on which we bought it, have contained 14.05 per cent. of morphine. Various tests which we made upon this sample from March, 1922, when it was first powdered, showed a steady diminution of morphine content until July, 1922. After that date the container was unopened for four months, and on testing in November, 1922, it was found to have begun to increase again in morphine content, until, when we commenced these experiments it had very nearly regained the strength which Harrison and Self had

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originally found in the opium, that is, of course, making allowance for the loss of water on drying. Indeed, if we allow for the fact that A. C. A.'s process necessarily gives a lower result than the B. P., amounting by our calculation to about 1.80th, it was rather stronger at this time than when they estimated it. Now, although each time we had opened this tin, either to take out samples for tests or for use, we had thoroughly shaken up the contents (or thought we had), when we commenced the series of experiments which we are now referring to, we not only shook it well, but knocked the bottom and sides so as to ensure that every particle should be equally mixed, and also because we wished to transfer the contents to a smaller vessel. To our surprise, however, when we came to pour it out for weighing we noticed that there were several aggregations, and, although we now see that we ought to have passed it all again through a sieve, we did not at the time think that these aggregations would or could, in any way, affect the result. They could in no way be called cakes, and the touch of a spatula reduced them to a uniform powder at once. Nevertheless, we believe that these aggregations have very seriously affected some of the samples into which they got.

We believe that these aggregations had been formed at the bottom corners of the tin, and been so completely covered with the other powder that they were not subjected to the free access of such air as the tin contained, as the other portion of the powder was, and that they had probably begun to gain in morphine content much sooner than the upper contents. We have not thought it fair to pick out and reject such anomalous results as we believe were due entirely to this cause, but we have not carried them into the column on which we rely for such conclusions as seem to us to be justified, and we have marked them as being abnormal, and we think that they should not be taken into account. We came up against this difficuly in the very first experiment which we made on series A.

The primary estimations made by us both showed the presence of 13.98 per cent. (average). Three months later J. R. found in one of this series only 13.28 per cent., whereas A. C. A. three days later found 13.64 per cent. This result was so anomalous that another test was made as soon as possible which showed 13.34 per cent., which confirmed J. R.'s first estimation. In the whole series of tests there are three or four entirely anomalous results and several which we think have been slightly affected by small portions of these aggregations getting in. However, fortunately in each series the first and last

results we believe to be practically correct, and in conformity with previous results, but we had not sufficient samples to spare for repetition.

It is well here to point out that all these samples which were put away in bottles for series A. B, C, D and E were jointly weighed, also that all tests were made by A. C. A.'s process (*P. J.*, April 29, 1922, p. 353) and not by the B. P., except where specially indicated the former eliminating the error due to evaporation during the process, and being therefore more definite.

Now we realised that it was not likely that our critics would be prepared to accept our explanation of the anomalous results found without some proof that our explanation was a sound one, and although we, on consideration, had no doubt as to the cause, we thought it desirable to test the accuracy of our view by a method which we had had in mind for some time. Fortunately, we had a stoppered bottle containing some pound and a half of powdered opium per 24 which had not been disturbed for some months. This was part of a lot of 7 lb. ¼ oz. bought as testing 11.48 per cent., and as it produced 5 lb. 9¼ oz. per 24, should then have tested 14.438 per cent. Forty ounces of it were used to make on this basis 577½ fl. oz. ($14.438 \times 40 = 577.52$) of tincture by A. C. A.'s process, which has been found invariably to remove as much morphine as the B. P. assay process. The opium, however, was later found only to test 14.30 (B. P. test), and it should therefore have made only 572 fl. oz. ($14.30 \times 40 = 572.0$), as it was, it tested only $0.984 = 0.994$ if it had been made to correct volume. These tests were mutually confirmatory.

About 1½ lb. of this remained. We took from the top of this bottle a sample and found it to contain 14.38 per cent., and having carefully removed the middle portion took another sample from the bottom. This tested 14.72 per cent., showing a difference of 0.34 per cent. between the top and bottom, or allowing for the fact that the upper portion contained 1.78 per cent. of water, and the lower only 1.46 per cent., viz., a difference of 0.32 per cent., the true figures would be 14.72 per cent. and 14.42 per cent., showing a difference of 0.30 per cent. The remainder of this opium was shaken up, and 20 oz. taken and made into tincture on the basis of an average of strength at the top and the bottom, viz., 14.55 per cent., and of perfect exhaustion as usual. This tested 0.992 per cent., confirming the tests of the opium.

It seems to us obvious what has happened. When the opium was

first put into the bottle a loss of morphine would commence, particularly at the top, and this would go on until, as the air present became vitiated, it would stop, and the reverse action would take place, commencing first at the bottom, where the air would probably not exceed in volume the opium itself (and could only be replaced by diffusion from the top), and later on at the top as well when the bulk of the air became so vitiated as to check the change. All these tests confirmed in our view the "working hypothesis" to which our previous work had led us. This powder had been in the tin from March, 1922, soon after which time the aggregations were probably formed, until September, 1923—say, eighteen months—and might easily have increased in strength from three to four times as much as the samples which we examined from the top and bottom of the bottle mentioned above—say, by 0.90 to 1.20 per cent.

We therefore consider that we are quite justified in supposing that portions of these aggregations were quite sufficient to account for the anomalous results referred to, and that they should be left out of account. We need hardly say that we should have liked to do the work all over again, but we are not running a research laboratory, and could not afford the time to do so, and our results must be accepted for what they are worth.

Let us now turn to the conclusions to be drawn from the results shown in the tables set out below. We propose first to deal with series A, B, D and E, of which unfortunately we only kept four samples each, and later with C, of which we kept eight.

Series A (full corked bottles). The loss per month in the first three months is at a greater rate than we have observed before, and actually greater than took place in series B in the same time, which is very remarkable unless bacteria have some influence, for series A were simply well corked, and series B were plugged with cotton wool.

TABLE A—FULL CORKED BOTTLES

Time in months	*Per cent. morphine*	*Per cent. morphine*	*Per cent. per month +or—from beginning*	*Per cent. per month +or—from last test*	—
At beginning	—	13.98	—	—	—
After 3 months ...	—	13.28	—0.23	—0.23	—
After 4 months ...	13.64	—	—	—	Abnormal
After 4 months ...	—	13.34	—0.16	+0.06	—
After 9 months ...	—	13.50	—0.05	+0.03	—

TABLE B—EXPOSED TO AIR

Time in months	*Per cent. morphine*	*Per cent. morphine*	*Per cent. per month +or—from beginning*	*Per cent. per month +or—from last test*	—
At beginning	—	13.98	—	—	—
After 3 months ...	—	13.40	—0.20	—0.20	—
After 6 months ...	13.46	—	—	—	Abnormal
After 9 months ...	—	12.94	—0.11	—0.07	—

TABLE D—KEPT IN CO_2

Time in months	*Per cent. morphine*	*Per cent. morphine*	*Per cent. per month +or—from beginning*	*Per cent. per month +or—from last test*
At beginning	—	13.98	—	—
After 3 months	—	13.65	—0.11	—0.11
After 7 months	—	13.48	—0.07	—0.04
After 11 months	—	13.40	—0.05	—0.02

TABLE E—KEPT IN OXYGEN

Time in months	*Per cent. morphine*	*Per cent. morphine*	*Per cent. per month +or—from beginning*	*Per cent. per month +or—from last test*
At beginning	—	13.98	—	—
After 3 months	—	13.39	—0.20	—0.20
After 7 months	—	13.38	—	—
After 11 months	—	13.34	—	—

Series E, however, which were treated with oxygen, showed almost the same loss in three months as series A, but whereas in series A the increase of strength had begun in six months and increased between the sixth and ninth month, in the case of series E after the loss sustained during the first three months, there was no change up to the eleventh month.

Series D (carbonic acid) simply point to the exclusion or partial exclusion of air retarding the loss. It is very probable that a good deal of air was not replaced by the CO_2, as we could not shake it up for fear of losing some of the fine powder. However, in view of the

new conditions and the small number of samples at our disposal, we do not think any definite conclusions can be drawn from A, B, D, or E.

Now, to turn to series C of samples heated in a water-oven to 98 degrees C. for two hours. This series we thought most likely to give us valuable information, and we fortunately kept eight samples, the estimation of which stretched over a period of twenty-one months. There was, as will be noticed, an immediate loss of 0.82 per cent. of morphine by the treatment; but after that, with the exception of the quite abnormal result at the seventh month, which we have excluded, there was no material alteration during the twenty-one months over which our experiments extended. These results not only satisfied us that opium could be sterilised at 98 degrees C., but satisfied us that the changes noticed were due to enzyme action. (*Vide infra.*)

Annett proved to his satisfaction the absence of all the enzymes for which he tested except oxydase and peroxydase, and the presence of the former seemed very doubtful. He, however, quotes Spence as finding both oxydase and peroxydase.—(*Bio-Chemical Journal,* 1922, Vol. 16, p. 766.)

TABLE C—HEATED IN WATER OVEN at 98° C.

Time in months	*Per cent. morphine*	*Per cent. morphine*	—
At beginning	—	13.98	
Immediately after treatment ...	—	13.16	—0.82, loss by treatment
3 months	—	13.11	
7 months	13.46	—	Abnormal
11 months	—	13.18	
15 months	—	13.16	
21 months	—	3.19	

In the series of tests which we gave in our paper published in *P. J.,* July 14, 1923, p. 28, Table 1, series A, which we reprint below in a clearer form, it will be seen that we give the results after heating in a water oven for two hours. Now this heating had been done by one of us, and it was noted that for some reason the thermometer showed that the temperature had never risen above 78 degrees C. We were at once doubtful whether the enzymes would be destroyed at this temperature, and it was only on the statement of the late

Professor Benjamin Moore in his elementary work "Origin and Nature of Life," p. 186, that enzymes "suffer rapid deterioration in all known cases at 50 degrees C. and at 60 degrees—70 degrees they are rapidly destroyed," that we felt justified in saying as we did, rather cautiously, that although presumably sufficient to destroy enzymes, has no influence in arresting the increase which under certain conditions takes place.

The conclusion to which we came at that time was entirely unjustified, as is shown by the fact that, although the treatment for two hours at 78 degrees in no way affected the morphine content of the sample so treated, the treatment in the later experiment at 98 degrees has seemingly entirely prevented change.

Table C shows that a temperature of 98 degrees C. causes an immediate loss of 0.82 per cent., but that no subsequent change takes place.

These facts strongly point to the destruction of an active enzyme between 78 degrees and 98 degrees C. of dry heat.

No doubt, when Professor Moore made this statement he was referring to enzymes contained in a liquid and not in a practically dry state; but, in any case, a great deal has been found out about enzymes since he published this little work. Race, in a paper on the Pasteurisation of Milk, published in *Chemistry and Industry,* Vol. 42, February 23, 1923, p. 166, gives the temperatures of destruction of peroxydase, of course, in a liquid, as taken by various authorities, as between 80 degrees and 83 degrees (times not given), but he himself gives 73 degrees in thirty minutes, and quotes Lythgoe as giving 75 degrees in thirty minutes. These, of course, being for a slightly acid liquid.

Now as neither of us was quite conversant with the more recent discoveries of bio-chemists in connection with the action of enzymes, a closer study of the subject became necessary if we were to get much further in this inquiry. We therefore consulted the works of Beatty and the more recent work "The Nature of Enzyme Action," by the late Sir William Bayliss, F. R. S., etc., 5th edition. These authors cleared away many of the difficulties which had confronted us, and showed that what had been mysterious to us was in reality a quite normal reaction of certain enzymes, and certainly of peroxydases. We had supposed that the decreases and increases of the morphine content of opium were probably due either to two enzymes acting more or less powerfully under different conditions, or (after we

thought that we had destroyed the enzymes at 78 C.) as possibly due to one enzyme and chemical action alone, *i. e.*, to Stoichiometric action, or, in other words, a chemical reaction not brought about by enzymes, ferments, or bacteria, although the latter seemed very difficult to accept.

As the study of enzyme action has not hitherto been covered by the Pharmaceutical curriculum, as it undoubtedly should be, we may, perhaps, with advantage, quote from Sir William Bayliss's work a few paragraphs which have a bearing on the subject. First, however, we think it should be realised that enzymes are catalysts and very powerful ones, and in this connection need only refer to any recent work on the subject.

The following are from Sir William Bayliss's work, fifth edition:

> P. 23: "If a catalytic reaction is destroyed by heat (60°-100°) it may be taken as practically certain that it is due either to living organisms or enzymes."
>
> P. 174: "So far as we know, the reactions catalysed by enzymes are reversible in nature, but since, as investigated *in vitro* they usually take place in an excess of water, the equilibrium position is very near the stage of complete hydrolysis. Owing to this reversible character of the reactions, it follows that enzymes have synthetic action. In the organism, mechanisms appear to be present which are able to diminish to a large extent the effective concentration of water, so as to favour the synthetic reaction where required."
>
> P. 53: "Heat increases activity before killing."
>
> P. 54: "If enzymes are catalysts, and if the reaction is a reversible one, the same agent which produces hydrolysis must also produce synthesis."
>
> P. 164: "A peroxydase alone without the presence of a peroxide is obviously of no use as an oxidising agent, so that the system of peroxide and peroxydase is the active combination. This system is, in fact, what is sometimes called an oxydase. In order that the process of oxidation may be continuous the peroxide component of the system must be capable of reformation by taking up oxygen again. Accordingly, we find that the oxidation of guaiacum by potatoes, for example, does not take place in the absence of oxygen."
>
> P. 6: "Catalysis of reversible reaction."

The question naturally arises, when the reaction catalysed is a reversible, or balanced one, has the fact that the equilibrium posi-

tion is arrived at under the accelerating influence of a catalyst any effect on the actual position of this equilibrium?

It was shown by Berthelot and Jéan de Saint Gilles (1862, p. 418) that if 1 molecule (= 1 Gm. mol.) of ethyl alcohol be mixed with 1 mol. of acetic acid, the reaction proceeds until the mixture has the composition:

1/3 mol. alcohol + 1/3 mol. acid + 2/3 mol. ester + 2/3 mol. water.

The same end position is also reached when 1 mol. of ethyl acetate is mixed with 1 mol. of water. So that in any mixture of these four bodies, two opposite reactions are proceeding at unequal rates, until a certain relative concentration of the constituents results at which point the two reactions have an equal velocity. Now suppose that a catalyst, *e. g.*, HCl is added to such a system, it is plain that unless both the opposite reactions were equally accelerated the equilibrium position woudl be changed.

"Again," p. 66, "it is found that synthesis takes place under conditions in which, according to the manner of reversible reaction, it would be expected to occur, *viz.*, high concentration of the products of hydrolysis."

We might, perhaps, with advantage, quote a good many other statements from Sir William Bayliss's work, but we think the above are sufficient to show that the changes observed by us in powdered opium are quite in accordance with recognised and established principles, although we realise that biologists and bio-chemists may, and do, differ in their explanation of observed phenomena.

To return to the conclusion to be drawn from Table C. We have pointed out above that the heating to 98 degrees C. caused a loss of 0.82 per cent. in the morphine content. Now, if we turn to Table 1, reproduced in a clearer form from our last paper, alcohol vapour test, at a temperature of about 55 dgerees C., we find that the loss was 1.07. This surprised us very much at the time, as the loss was greater than was caused by heating in an air-oven at 114 degrees-115 degrees C. It would almost seem as if the alcohol vapour treatment had stopped the synthesising activity of the enzyme, and as usual had stimulated its hydrolising activity before destroying it. We thought at the time that the figures pointed to the alcohol vapour not having been efficient in destroying the enzyme, and such may have been the case, but it may have been efficient in destroying the enzyme in that case also.

TABLE I—FROM PAPER PUBLISHED JULY 14, 1923 (p. 29)
24 POWDER BY A. C, A.'s PROCESS

——	*Per cent. found*	*Loss or gain per month since last test*
Untreated av. 4 tests, April 4 to 28, 1922	13.52	—
Do. July	13.39	—0.05
Do. November	13.72	+0.08
Heated in water oven at 78° C. only av. of 2 tests*	13.70	—
Air oven 114-115° C., 2 hours* ..	13.28	Immediate loss 0.44 per cent.
Alcohol vapour, av. of 2 tests* ..	12.65	Immediate loss 1.07 per cent.

*Experiments November, 1922.

The fact that the air-oven treatment actually caused a smaller loss, *viz.*, 0.63 per cent., at first sight seems absolutely contradictory to this view, but is not really so as the dry heat in that case, by rapidly removing the water may have very rapidly stopped the hydrolysis to which the loss is due (or/and) have killed the enzyme before it had time to exert its dying activity.

Annett, *J. S. C. I.*, Vol. 37, 1918, gives a number of tables showing the effect of heat upon opium. He found that a sample of *moist* opium tested by B. P., 1914, lost 0.87 per cent. of morphine when heated in a water oven for six days, but he found no such effect in a shorter period, but these results are not in agreement with figures given in other tables in the same paper. For example, two samples heated in the same way for twelve days, had lost in six days more than twice as much as in the above case, *viz.*, average of 1.902 per cent., and again in another case after forty-eight hours' similar treatment there was a *gain* on an average of three estimations of 0.32 per cent. Now, these results, which on first sight are so contradictory, are no doubt quite explainable. Now, whether we accept either the one view or the other held by biologists on this subject, it is abundantly clear that hydrolysis cannot go on when all there is to hydrolise has been hydrolised, and it is equally clear that synthesis cannot go on beyond a similar point.

It is therefore obvious that what happens when a sample of opium is treated in any way must depend upon which change has been taking place, and also how far such change has gone. That is to say, that if the conditions previously prevailing have favoured one

of the reactions, and repressed the other, the reversing of the conditions will naturally favour the reversing of the reactions.

We think we have seen it stated that opium taken in the morning from the capsules is not of the same strength as that obtained at night, but we cannot turn up any authority for this, nor do we know at which period it is strongest. However, we know enough of the growth of plants, and the way they behave during the day and the night to say that such a thing is not only possible, but almost certain.

Conclusions

The conclusions to which we have come from the results of experiments recorded in this and previous papers and the papers of Messrs. Annett and Singh are:

1. That opium contains an enzyme which is a peroxydase, and is destroyed in a powder containing from 1 to 2 per cent. of water at a temperature of 98 degrees C., and which we suggest should be called opiase.

2. That the changes in the morphine content are due to this enzyme.

3. That powdered opium before being used for pharmaceutical purposes should be heated for two hours at a temperature of 98 degrees to 100 degrees C., and, after adjusting to contain 10 per cent. of anhydrous morphine, be stored in small bottles closed with well-fitting paraffined corks.

4. That the supposed difficulty of obtaining concordant results by different analysts or even by the same, are, so long as the analysis is honestly done by a good process and a competent analyst, entirely due to changes caused by this enzyme, and that there is no other reason why results should not be as concordant as in the case of other analyses.

5. That the process of the B. P., 1914, is a very easy and satisfactory one for ordinary purposes, where an error either way of one-half per cent. is permitted, but that it can be increased in accuracy and completed in less time if the modifications named below are adopted, and that in the case of research work when greater accuracy is required such variations as those suggested below are essential.

6. That the chief sources of error in the B. P. process are due (*a*) to loss of water during the trituration in the mortar and the

subsequent filtration, which will vary with the time occupied, and the temperature of the air and its dryness.

(*b*) To errors in measurement of the amount of filtrate taken for estimation.

(*c*) To passing the ethereal solution through the filter paper before the aqueous liquid is put on.

(*d*) To errors in titration of the morphine.

(e) That the drying of the morphine at 110 degrees C. in unnecessary, and that a perfectly definite compound is obtained if drying at 60 degrees to 70 degrees is employed, and that by deducting 1/14 from the weight of morphine thus obtained (for remaining water and a minute amount of impurities), the net amount of anhydrous morphine present is found with as great accuracy as by drying to 110 degrees C. and titrating, and in the case of anyone not constantly carrying out the process even greater.

We need hardly point out that if our process is not strictly carried out, the morphine must be titrated. For instance, if the opium is previously deprived of its resins and waxes, it is purer and must either be titrated or a different deduction made.

It should also be noted that we do not say that powdered opium heated for two hours at 98 degrees C. will never subsequently change, as there are doubtless moulds or their spores, or possibly bacteria, which may affect it as they might not be destroyed at that temperature, or may get in subsequently, but if properly preserved in well-closed vessels, we believe that no material change will take place.

The Estimation of Morphine in Opium

All chemists are agreed that *cæteris paribus* a gravimetric analysis is to be preferred to a volumetric one, but the much greater convenience and rapidity of the latter has by the adoption of very dilute volumetric solutions and very accurate and delicate burettes, together with more delicate indicators, removed this objection and put volumetric analysis on a very high level of accuracy, and in some cases even above the gravimetric. Many years ago, before burettes had been brought to their present level of perfection, standard solutions were *weighed,* not *measured,* and, of course, theoretically, it is the more accurate method, although now for all practical purposes unnecessary.

The B. P. process is a mixture of the gravimetric and volu-

metric, and contains the weaknesses of the latter, which the details given below are designed to remove.

We have made various experiments to find what actual errors may arise from the causes we have named above, and give them below:

—	—	*Causing an error on a 15 per cent. opium of*
Loss of water during trituration, etc., may amount to	1/80 more or less	0.18 per cent.
Not washing out measure after opium solution	1/40	0.375 per cent.
Employing wet measure	—	about the same

We, of course, have not included errors due to inaccurate measures, of which there are plenty about (we are afraid of English make), nor to the employment of pipettes made to *deliver* and not to *hold,* a given quantity. The latter error is very easily made, as makers do not indicate how they are graduated.

Our recommendation to reduce the time of maceration from eighteen hours to half an hour (as originally recommended by A. C. A.) is based on the following experiments, but for research we should prefer the longer time.

EXPERIMENTS MADE BY J. R. BETWEEN DECEMBER 29, 1923, AND JANUARY 8, 1924

Time of maceration	*Per cent. found*
½ hour	13.39
24 hours	13.46
24 hours	13.46 (given 48 hours to crystallise)
40 hours	13.42

Process for estimation of morphine in opium, as suggested by A. C. A. in *P. J.,* April 29, 1922, page 353, slightly varied in detail:

Opium in 24 powder	8 Gms.
Glass in 40 powder	2 Gms.
Calcium hydrate	2 Gms.
Distilled water	40 Cc.

Rub in glass mortar until the opium is mostly reduced to an impalpable powder. Add 20 cc. more distilled water and again rub well. Allow it to settle. Grease the lip of the mortar, and decant the liquid mixed with the finer powders into a 4 oz. tared, wide-mouthed, stoppered vessel. Rub the remaining coarser particles with 15 cc. of distilled water until all is reduced to a very fine state, and add it to the first portion, scraping out as much as possible with a small steel spatula. Repeat this with 5 cc. of distilled water, and again with sufficient to make the contents of the bottle weigh 92 gms. Allow this to macerate, with occasional agitation, for half an hour. Filter off into a bottle graduated on neck to 51 cc., using a covered funnel. Transfer to a suitable vessel, and wash out the 51 cc. bottle first with 5 cc. 90 per cent. alcohol and afterwards with 25 cc. of ether, and add the washings to the opium solution. Add 2 gms. chloride of ammonium. Shake well, and set aside for twelve hours, shaking occasionally. Draw off the supernatant ethereal liquid (which should be quite free from crystals) by means of a pipette and reject it.

Rinse the vessel with 10 cc. of ether by a gentle rotary motion. When separated, remove this as before, and reject.

Counterbalance two small filters of about 90 mm. diameter, place one within the other in a small funnel in such a way that the triple fold of the inner filter shall be superimposed upon the single fold of the outer filter.

Transfer the crystalline morphine from the vessel by means of the pipette to the filter, adjusting this to the sides of the funnel, if necessary, with it; remove all the liquid in the same way, removing any crystals adhering to the vessel by means of a glsas rod slightly curved at the end, and covered also at the end with a little india-rubber tubing project one-eighth inch beyond it.

When all the liquid has passed through, wash the remainder of the morphine from the vessel with morphinated water until the whole has been removed. Wash the crystals with morphinated water until the washings are free from colour; allow the filters to drain, and dry them by pressing gently between several folds of filter paper and then between 60 degrees and 70 degrees C. separately.

Weigh the crystals in the inner filter, counterbalancing by the outer filter. Deduct from the weight found 59/800, practically 1/14, and add to it for loss during process 0.051.

The figure thus obtained multiplied by 20 will give the percentage of morphine in the sample.

I recommend this process because what is wanted is a process as simple as possible with due regard to accuracy, and one which will, in the hands of different analysts, give practically the same results.

I claim to attain this.

First, by using glass, to ensure that the opium, in whatever fineness of powder it may be, can be reduced to a very fine powder indeed.

Second, by doing this in a closed vessel, to avoid evaporation.

Third, by rejecting the ether-alcohol liquid, and thus removing one very fruitful source of error.

Fourth, by omitting the titration which, if the analysis has been properly conducted, always produces the same results, as far as decinormal solutions can show.

My figure of 59/800 for deduction from crude morphine found is based on 6.5 cc. used for 0.2 gm. dried between 60 degrees and 70 degrees C.

MEDICAL AND PHARMACEUTICAL NOTES

WHAT IS AN ANTISEPTIC?—The word "antiseptic" is used loosely enough in this country as in America. The finding of the U. S. Bureau of Chemistry, which administers the Food and Drugs Act (*P. J.*, July 2, p. 21), that the term is "objectionable" unless the medicinal product to which it is applied destroys micro-organisms when used as directed, is of interest. Apparently the Bureau deprecates, and possibly later on will prohibit, the application of the term "antiseptic" to a number of preparations such as mouthwashes, sprays and gargles, which are widely advertised, and which by reason of their dilution and their brief contact with the part to which they are applied, cannot produce a condition of real antisepsis. The *Prescriber* points out, however, that although investigators say that certain drugs "possess little or no antiseptic action," it is known that such drugs

administered in cases of intestinal trouble quickly produce a cessation of the symptoms, and undoubtedly arrest the growth of offending organisms. "Something similar undoubtedly takes place in the case of antiseptic mouth-washes and nasal douches, and it is hardly fair to stigmatise all such preparations as useless when clinical experience has shown their value over and over again." This is a point of view which the American Bureau has, perhaps, overlooked.—(*Criticus: Pharm. Jour.*)

Tooth-Brush History—It has been suggested that the tooth-brush, that essential of oral hygiene, such large numbers of which are sold nowadays, is a product of the last hundred and fifty years. Probably the convenient type of brush with which we are familiar is comparatively modern, but the use of a brush for the teeth appears to have been a recognised practice in the twelfth or thirteenth centuries. The Code of Health of the School of Salerno (*Regimen Sanitatis Salernitanum*), written for popular information by professors of the famous school, contains the following advice:

> At early dawn when first from bed you rise,
> Wash in cold water, both your hands and eyes.
> With brush and comb then cleanse your teeth and hair,
> And thus refreshed, your limbs outstretch with care.

Possibly the apothecaries of Salerno stocked and sold the mediæval equivalent of our prophylactic brushes for the teeth.—(*Criticus: Pharm. Jour.*)

Medical Discoveries by Young Men.—William Harvey described the circulation of the blood in 1628, at the age of fifty.

Thomas Bartholinus described the existence of the thoracic duct in 1652, at the age of thirty-six.

Jan Swannerdam observed red corpuscles in frog's blood in 1658, at the age of twenty-one.

John Abernethy was the first to ligate the external iliac artery for aneurys min 1796, at the age of thirty-two.

Ephraim McDowell performed the first ovariotomy in 1809, at the age of thirty-eight.

Joseph Priestley discovered nitrous oxide in 1772, at the age of thirty-nine.

René Laënnec invented the stethoscope in 1815, at the age of thirty-four.

Crawford W. Long performed the first operation with the patient under the influence of ether in 1842, at the age of twenty-seven.

William Thomas Green Morton used ether in 1846, at the age of twenty-seven.

Lord Lister communicated his successful results in antisepsis to a meeting in 1867, when he was forty years of age. He had graduated twelve years before.

Robert Koch discovered the tubercle bacillus in 1882, when he was thirty-nine years old.

Von Behring first used diphtheria antitoxin in 1890, when he was thirty-six years old.

Frederick Banting discovered insulin in 1923, when he was thirty-one years old.

Madame Curie did her work on radium in 1899, when she was thirty-two years old.

Darwin did his work on the origin of species at twenty-nine years, and Wallace his at thirty-six years.

Pasteur's epoch-making discoveries started with his work on ferments when thirty-five years old.

Servetus published his discovery of the blood circulation when forty-four years old.

Eustachius completed his anatomic tables when twenty-eight.

Vesalius swept away Galen's anatomic errors with his Fabrica when twenty-nine years old.

Fallopius completed his remarkable discoveries before he died at thirty-nine.

Ehrlich discovered mast cells and began his stain work when twenty-three years old.

Paré performed the first exarticulation of the elbow when twenty-six and published his book on gunshot wounds when thirty-five.

Jenner began his observations on vaccination when not yet thirty.

Lavoisier discovered oxygen when thirty-two.

Neisser discovered the gonorrhea bacillus when twenty-four, and Schaudinn *Spirochaeta pallida* when thirty-four.

Bichat published his treatise on membranes when twenty-eight.

Semmelweis recognized the infectiousness of puerperal fever when twenty-nine.

Skoda systematized percussion and auscultation when thirty-four.

Widal suggested his typhoid test when thirty-four.

Claude Bernard, when thirty, had already started his study of the glycogenic function of the liver.

Von Helmholz, at twenty-six, had already established the law of conservation of energy.

Du Bois-Reymond, at twenty-five, discovered the difference of potential between the cut and the uninjured ends of an excised muscle or nerve, and defined electrotonus.

Velpeau published the first detailed work on surgical anatomy when twenty-eight.

Carl Ferdinand von Graefe, when twenty-nine, devised the operation for cleft palate and founded modern plastic surgery, and his son Albrecht described keratoconus when twenty-six and introduced iridectomy in several eye conditions when twenty-seven.

Bell began publishing his anatomy when thirty.

Hodgkin described the disease still bearing his name when thirty-four.

Ricord established the differentiation of gonorrhea and syphilis when thirty-two.—(*Jour. Amer. Med. Asso.*)

Removal of Mercurochrome Stains from Clothing—Prepare a saturated solution of Oxalic Acid. Mix with equal parts of Hychlorite or Zonite (or any other solution of Sodium Hypochlorite) and immediately dip the stained clothing in the mixed solution. The nascent Chlorine gas will remove the stain. Caution should be used that the original color of the cloth is not affected by Chlorine. —G. K.

New German Anæsthetics—German scientists in their search for improved anæsthetics that do not have to be administered through inhalation, have developed at least three narcotics that deserve more than passing notice.

E 107, known also as Avertin, owes its existence to Willstaedter (Munich) and Sauerbruch (Berlin) and is produced by Willstaedter and Duisberg of I. G. Farbenindustrie A. G., Frankfort on the Main. It is a tribromal-alcohol, producing narcosis through the intestines.

Another new anæsthetic is so-called Pernokton, reported by Professor Dr. Bumm at the recent surgeons' congress in Berlin. It is related to Barbital and is injected into the veins, thus reaching sensitive parts through the blood circulation.

Lumbalanæsthesin is another that is administered through the spinal cord and is capable of anæsthetizing the lower half of the body particularly, but this form of administration is reported not altogether harmless.

Research continues to seek anæsthetics freed from the inconveniences of inhalation with probable eventual success.—*Trade Commissioner W. T. Daugherty, Berlin, Germany.*

SCIENTIFIC AND TECHNICAL ABSTRACTS

FEDERAL CAUSTIC POISON ACT.—"An Act to safeguard the distribution and sale of certain dangerous caustic or corrosive acids, alkalies, and other substances in interstate and foreign commerce" was approved by the President on March 4, 1927 (Public Document No. 783, 69th Congress, 6 pages). This Act may be cited as the "Federal Caustic Poison Act." The term "dangerous caustic or corrosive substance" is applied to hydrochloric acid, sulphuric acid, nitric acid, carbolic acid (phenol), oxalic acid, oxalates, acetic acid, free or combined hypochlorous acid, potassium hydroxide, sodium hydroxide, silver nitrate, ammonia water, and certain of their preparations including those containing 20 per cent. or more of free or chemically unneutralized acetic acid; 10 per cent. or more of oxalates, or of free or chemically unneutralized hydrochloric acid, sulphuric acid, oxalic acid, potassium hydroxide or sodium hydroxide; 5 per cent. or more of silver nitrate, phenol, or free or chemically unneutralized nitric acid or ammonia, and preparations (other than calx chlorinata, bleaching powder, and chloride of lime) yielding 10 per cent. or more by

weight of available chlorine. The retail parcel, package, or container of a dangerous caustic or corrosive substance is misbranded unless it bear a conspicuous, easily legible label containing the common name of the substance, the name and place of business of the manufacturer, packer, seller, or distributor; the word "poison," and, if intended for household use, directions for treatment in case of accidental personal injury by the substance. Misbranded parcels, packages and containers of these substances are denied shipment in interstate or foreign commerce. However, exports may be branded in accordance with the laws of the foreign country. Provision is made for the exclusion of misbranded imports; and penalties are provided for violations of the Act. The enforcement of the Act is placed in the hands of the Secretary of Agriculture. The Act became effective upon its passage, but the penalty and condemnation clauses concerning violations are effective six months thereafter.—(*Jour. Frank. Inst.*)

NEW UNIVERSAL INDICATOR—Emil Bogen, of the University of Cincinnati (*Jour. Am. Med. Asso.*, 1927, **89**, 199), has devised the following universal indicator for use in the colorimetric determination of hydrogen-ion concentration: Phenolphthalein 0.100 gram, methyl red 0.200 gram, dimethylaminoazobenzene 0.300 gram, bromthymol blue 0.400 gram, thymol blue 0.500 gram, absolute alcohol 500 cc. The indicators are dissolved in the alcohol; and tenth-normal sodium hydroxide is added to the resulting solution until it becomes yellow in color. In order to determine the hydrogen-ion concentration of a solution, one drop of the universal indicator is added to one cubic centimeter of the solution; a red indicate pH 2.0, orange pH 4.0, yellow pH 6.0, green pH 8.0, blue pH 10.0. These values are approximate; more exact values may be obtained by comparison with buffer solution of known pH to which the universal indicator has been added. Differences as low as 0.2 of a pH unit may be distinguished.—J. S. H.

NEW REACTION FOR COBALT—Cobalt in strongly ammoniacal solution gives a yellow, orange, or red color with sodium thiosulphate, or a brownish black precipitate according to the concentration of the Cobalt. A dilution of 1 of Co in 100,000 can be detected thus. The blue color of an ammoniacal solution of Ni is unchanged by the

reagent, but when much Co is present the color is violet-blue; it is then decolorised on adding formaldehyde solution, which may cause the green color of the Ni to reappear. When Co is accompanied by other metals, the filtrate obtained after adding the sodium thiosulphate is reddish yellow, deepened on adding more of the reagent.—P. Falciola (*Giorn. Chim. applic.*, 1926, **8**, 612 through *Brit. Chem. Abstr.*, A., 1927, 332.)

Test Garage Air for Deadly Monoxide Gas—How great is the danger of carbon monoxide poisoning to which garage employes are exposed? We read frequent accounts in the daily news about automobile owners who have committed involuntary suicide in their small private garages by running the engines when the doors are shut. Yet mechanicians work all day behind closed doors in large garages. How much of an industrial hazard are they exposed to?

Dr. S. H. Katz of the U. S. Bureau of Mines, and Dr. H. W. Frevert, of the U. S. Department of Agriculture, have been endeavoring to find an answer to these questions, and they reported on their work before the meeting of the American Chemical Society in session recently.

The two investigators collected samples of the air from a large Government garage in Washington and from a large commercial garage in Pittsburgh, and subjected them to chemical analysis. They found that the working conditions in the Government garage, so far as the poisonous gas was concerned, were better than those in the commercial establishment. During the regular working day the concentration in the Government garage never exceeded one part of carbon monoxide in ten thousand parts of air, while in the Pittsburgh shop th maximum was two-thirds again as much, or 1.64 parts in ten thousand.

In neither establishment did the concentration reach the danger point, though during one hour the carbon monoxide in the Pittsburgh garage attained a "bad eminence" of 4.33 parts per 10,000 of air. This, it was stated, is enough to cause headache in some men.

The report adds, however, that the investigations were conducted under only average working conditions. In very cold winter weather, when the garage doors are likely to be kept more tightly closed, conditions may become more serious.—*Science Service.*

NEWS ITEMS AND PERSONAL NOTES

BOTANICAL GARDENS A BEAUTY SPOT—The experimental gardens of the Philadelphia College of Pharmacy and Science, at Glenolden, Pa., have presented a beautiful picture during the past few months. Established about six years ago, they have now reached a state of development where they are not only beautiful to look upon, but of real practical value and interest to the student of botany, particularly of medicinal plants.

The gardens are conducted in connection with the drug farms of the H. K. Mulford Company, through whose generous interest and co-operation this venture was made possible. Students of the Philadelphia College of Pharmacy and Science, as well as of other institutions, and also many other botanists, pharmacists and physicians have been using the gardens for study in increasing numbers. More than 350 different varieties of plants are growing there.

Pharmacists and physicians visiting Philadelphia should get in touch with the Mulford Laboratories while in the city and arrange for a visit to these very interesting gardens and laboratories.

PROF. JOHN C. KRANTZ, JR., WITH SHARP & DOHME—On August 1, 1927, Prof. Krantz assumed the directorship of the Pharmaceutical Research Laboratories of Sharp & Dohme, and his many friends and co-workers in scientific research endeavors will doubtless wish for him a brilliant future in his new field.

He is well equipped, by training and experience, to adequately fill his new and exacting position. His preliminary education was obtained in the public schools of Baltimore and the Baltimore City College, from which he graduated in 1916. In 1919 he completed his course in pharmacy at the University of Maryland, and in 1920 was granted the degree of Ph. C. by his Alma Mater. After completing advanced studies at University of Maryland and Johns Hopkins University, he was awarded the additional degrees of Phar. B., M. S., and Sc. D.

Since 1921 Prof. Krantz has continuously held various responsible teaching positions in the departments of Pharmacy and Dentistry, University of Maryland the Hospital and Medical Department of Johns Hopkins University. From 1925 until the present he has filled the chair of Professor of Pharmacy, at the University

of Maryland. Along with his new work with Sharp & Dohme, Dr. Krantz will continue his connection with Johns Hopkins University as consultant pharmacist to the hospital and lecturer in chemistry and pharmacy in the training school for nurses.

Prof. Krantz has been at all times an active member of the various scientific bodies that are working for advancement in the field of pharmacy and pharmaceutical research. In 1924 he was the recipient of the A. Ph. A. research grant.

M. EMILE PERROT, professor of pharmacy in the University of Paris, has been elected a member of the Paris Academy of Medicine.

PROMINENT ENGLISH PHARMACISTS VISITING AMERICA—The president of the society (Mr. Herbert Skinner, Ph. C.) and Mr. Thomas Marns (member of the Council) spent their holidays in Canada and the United States. Their itinerary included Montreal, Toronto, Niagara, Buffalo, Detroit, Chicago, Washington, Philadelphia and New York. They return from Boston in the "Cedric" on September 25, and are due back in Liverpool on October 3. Though their tour is entirely private and does not embrace any official functions, an interesting round of visits has been planned for them, which, it is certain, will still more strongly cement the bonds of friendship between the pharmacists of Great Britain and those of the New World.

BOOK REVIEWS

KOLLOIDCHEMISCHE TECHNOLOGIE. Ein Handbuch Kolloidchemischer Betrachtungsweise in the chemischen Industrie und Technik. Unter Mitarbeit von Autoritäten Herausgegeben von Dr. Raph. Ed. Liesegang, Frankfurt A. M. Lex. 1047 pp. mit 419 Abbildungen und Zahlreichen Tabellen. Cloth 70 Mk. Verlag von Theodor Steinkopff, Dresden & Leipzig.

Colloidal Chemistry, the youngest child of mother chemistry is the binding tie, or as Dr. Jerome Alexander, an authority on this subject, so properly expresses himself, the "dawn" between physics and chemistry. It was a Britisher, Thomas Graham, F. R. S., Master of the Mints, who became father of colloidal chemistry through

his studies on the diffusion of substances through animal membrane. His paper "Liquid Diffusion Applied to Analysis," read on June 13, 1861, before the Royal Society of London, laid the cornerstone to the new science.

The book before us deals with Colloidal Chemistry in Technology. The author and his collaborators are experts on this subject and consequently an authentic book, a masterwork was created. The division is the following:

I. Theoretical Part containing among other subjects Colloidal Solutions, Dialysis, Ultrafiltration, Electro-Osmosis, Viscosimetry, Capillary Analysis, etc.

II. Special Part. Among the twenty-eight subjects treated, I will mention the following, of special interest to the pharmacist: Ink, Soap, Paper, Glass, Emulsions, Glue and Gelatine, Adhesives and Photography. Each monograph is written by an authority on the particular subject and is complete in itself and is based not only on theory but practice! This last point is one of the principal advantages of the work. As to be expected from a book of this kind it abounds in references, as many as 5 (p. 835), 6 (p. 944), 10 (p. 9), and even 11 (p. 19). This is another proof of its thoroughness.

The author and his assistants have made an enviable record in research of this field of chemistry and are, consequently, well qualified to speak as authorities. The material covered is the result of their own investigations and the book can therefore justly be pronounced as a "masterwork."

OTTO RAUBENHEIMER, Ph. M.

PHARMACEUTICAL BOTANY. By Heber W. Youngken, A. M., Ph. D., Massachusetts College of Pharmacy. 5th edition, xxvii-692 pages, 387 illustrations and glossary of botanical terms, small 8vo. Philadelphia, P. Balkiston's Son & Co.

Dr. Youngken's book has been before the pharmaceutical profession for many years. It early acquired a prominent position which it has maintained uninterruptedly. The fact that five editions have been required is proof that it serves fully a wide application. The present edition represents an enlargement and covers a very extensive field of botany, both as regards the classifications of plants and the structures, macroscopic and microscopic. Treating first of the gen-

eral characteristics of plants, that is, the plant as a living entity and the groups thereof, the technique of plant examination is then treated extensively. Information is given as to the use of the microscope, the principles of its construction, directions for its care, the making of sections and the technique of staining and making permanent mounts. Descriptions of the great groups in their structural relations then follow with the life history of a fern as an initial type. Full discussion is given to the structure of the cell and to the various forms of cell contents including the carbohydrates, the glucosides, the alkaloids, fatty and resinous matters, pigment and mineral deposits. Structure of cell walls is then described. A discussion of the general nature of plant tissues such as cork and bark is included. The various developments in the morphology of the plant are then given extensive description—the leaf, the inflorescence, the flower, the fruit and the seed.

Principles of classification are then taken up with a review of the more important systems that have been suggested in this field. General descriptions of the great groups follow beginning with the algæ and terminating with the monocotyledons. A chapter on ecology, a subject which is now attracting a great deal of attention by botansts, follows and then a special description of the more important features of the carnivorous plants. Dr. Youngken has given a great deal of special attention to this field and presents the latest information available.

The book will constitute a complete introduction to the general field of structural and systematic botany.

HENRY LEFFMANN.

WITH LASALLE, THE EXPLORER. By Virginia Watson. Illustrations by Henry C. Pitz. 366 pp. Cloth $2.50. Harper & Brothers, 49 E. Thirty-third Street, New York City.

On previous occasions (Pharm. Zentralhalle Vol. 66 No. 29 and Medical Life Am. Pharmacy Number, Feb. 1926) the referee in his "Early History of Pharmacy in America" wrote in the chapter on French colonies: "The itinerant Jesuit missionaries became also physicians and pharmacists. The French Franciscan missionary and explorer Louis Hennepin (1640-1706) came to Canada in 1675, joined LaSalle in 1678 and on April 11, 1680 was captured by the Sioux Indians, adopted as one of their tribe, learned their customs

including remedies and medicines and then escaped in 1681. Robert Cavallier Sieur de la Salle (1643-1687), the famous French explorer in North America, in 1682 passed down the Illinois and Mississippi Rivers to the Gulf of Mexico, taking possession of the land for Louis XIV and naming it in his honor Louisiana. In his contact with the natives LaSalle also became acquainted with their remedies and practices."

The book before us is a historical fiction of a sort that makes history a highly interesting study. In twenty-five chapters are told the travels and explorations of LaSalle from Quebec up the St. Lawrence, through Lake Ontario, Lake Erie, Lake St. Claire, Lake Huron, Lake Michigan and down the Illinois River and the Mississippi to the Gulf of Mexico which was reached on April 9, 1682. This last scene adorns the cover of the book together with La Salle's own words: "In the name of the most high, mighty, invincible and victorious Prince, Louis the Great," the beginning of his speech when taking possession of the land. It may be new to learn that it was La Salle's desire to discover a water route to China and thus open to France the way to trade with them for their fabulous riches. On his second exploration La Salle sailed from France, landed in the Bay of St. Louis or Matagorda Bay. Here his fate reached him as most of his men rebelled and he was shot by Liotot, the surgeon on his ship. Among the interesting chapters of the book I will mention: "The Medicine Bag of Old Wolf, Chief of the Seneca Indians," which was found by one of La Salle's companions. An excellent map of La Salle's explorations 1669 to 1687 accompanies the book and greatly helps to elucidate the text.

OTTO RAUBENHEIMER, Ph. M.

OLD CHEMISTRIES. By Edgar F. Smith, University of Pennsylvania. Lex., 89 pp. 32 Illustrations. $2.50. McGraw-Hill Book Co., Inc. 370 Seventh Ave., New York City. 1927.

Only a short time ago, in February, 1927, Prof. Charles H. La Wall in his masterwork "Four Thousand Years of Pharmacy" described many "Old Pharmaceutical Books" and reproduced their title pages as illustrations. Just off the press is the book before us entitled "Old Chemistries" from the pen of Prof. Edgar Fahs Smith, the Father of History of Chemistry in the United States.

The book is divided into three chapters arranged as to periods:

I. Begins with *Alchemiae Geberi Arabis* 1542 and ends with *Historie de la Philosophie Hermetique,* 1742.

II. Commences with *Syllabus of a Course of Lectures on Chemistry,* by Benjamin Rush, M. D., 1770, up to *Plain Discourses,* by Thomas Ewell, M. D., 1806.

III. (Unfortunately the heading "Chapter III." is missing on page 52.) Begins with *Chymical Catechism,* by Samuel Parkis, 1806, and ends with *System of Chemistry,* by Franklin Bache, M. D., 1819, well known in pharmacy circles as one of the fathers of the U. S. Dispensatory.

Among the thirty-two excellent illustrations we want to point out the following portraits of men who should be well-known in pharmacy: Benjamin Rush, Hermann Boerhaave, Fourcroy, Lavoisier, Chaptal, Bergmann, Frederick Accum, Silliman the Elder, Robert Hare, Joseph Black and Franklin Bache. While the referee is well aware that the space for illustrations is limited, may he suggest that the next edition of this valuable book will include portraits of Antoine Baumé and the two American chemists: Thomas Cooper and James Cutbush, the Philadelphia apothecary and chymist.

The book has the object to bring before interested readers a hint of the vast stores of early literature relating to chemistry, of which many are ignorant, totally ignorant. Let us hope that this volume will elicit further search and research along similar lines.

The author's hope is that sometime—how soon he knows not—but, sometime—the history of chemistry will be given its place in the curriculum of studies in every institution of learning where this science is studied. To this the referee will add, as he has advocated for many years, that history of pharmacy will be given a place in our College of Pharmacy! The two studies could be combined, as both subjects are intimately interwoven, in fact "Pharmacy is the Mother of Chemistry!"

Otto Raubenheimer, Ph. M.